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(54) Prodrugs of phosphonates.

(57) There are disclosed novel oral prodrugs of phosphonate nucleotide analogs which are hydrolyzable under physiological conditions to yield compounds which are useful as antiviral agents, especially as agents effective against RNA and DNA viruses. They may also find use as antitumor agents.

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The present invention relates to novel orally active prodrugs of phosphonate nucleotide analogs, their pharmaceutically acceptable acid addition salts, a process for their production, and to their use. The prodrugs of the present invention exhibit antitumor activity and a broad spectrum of antiviral activity.

Infectious viral diseases are recognized as an important medical problem. Progress against infectious viral diseases requires the development of drugs with selective antiviral activity while remaining benign to normal cell lines. Among the antiviral agents currently under study, which seem to possess selectivity, are phosphonate nucleotide analogs. In general, these compounds are structural analogs of the monophosphates nucleoside analogs.

A number of phosphonate nucleoside analogs have been described in the literature. These nucleoside analogs have been described as potent and selective antiviral agents with activity against a broad spectrum of DNA and RNA viruses.

For example, 9-(3-hydroxy-2-phosphonylmethoxypropyl (HPMP) and (2-phosphonylmethoxy)ethyl (PME) analogs of purine (adenine (A), guanine (G), 2,6-diaminopurine (DAP), 2-monoaminopurine (MAP), hypoxanthine (Hx) and pyrimidine (cytosine (C), uracil (U), thymine (T) were evaluated for antiviral properties. (S)-HPMPA, (S)-cyclic HPMPA, (S)-HPMPC, (S)-HPMPG, (S)-HPMPDAP, PMEDAP, PMEG and PMEA were active against herpes simplex virus, type 1 and 2 (HSV-1 and -2). (S)-HPMPA and (S)-cyclic HPMPA were active againt varicella zoster virus (VZV). (S)-HPMPC was active against human cytomegalovirus (HCMV), a common cause of opportunistic infection in AIDS patients. (S)-HPMPA and (S)-cyclic HPMPA are active against adenovirus and vaccinia virus. PMEA, PMEDAP, and PMEMAP are active against human immunodeficiency viurs (HIV), the human retrovirus responsible for AIDS. De Clercq, et al, Antiviral Research, 8: 261-272 (1987).

Bronson, et al., report on the series of acyclic nucleotide analogs having a common PME side chain attached to a purine or pyrimidine base which were prepared and selected for in vivo antiviral activity against retroviruses and herpes viruses. The adenine analog, PMEA, showed good in vitro activity against HIV and Rauscher murine leukemia virus (R-MuLV), and was more potent in vivo than 3'-azido-3'-deoxythymidine (AZT) in the treatment of R-MuLV in mice. PMEA also had a significant antiviral effect in vivo against murine cytomegalovirus (MCMV), and in vitro activity against HCMV. The guanine analog, PMEG, was exceptionally potent in vitro against herpes viruses. In vivo, PMEG was >50-fold more potent than acyclovir against HSV 1 infection in mice. Nucleotide Analogs as Antiviral Agents; ACS Symposium Series 401; Martin, J. C. Ed.: Washington, DC, 1989, Chapter 5, pp. 72-87. Kim, et al., in J. Med. Chem., 33: 1207-1213 (1990), describe a similar series of compounds.

De Clercq, et al, in Nature, 323: 464-467 (1986) state that (S)-HPMPA has potent and selective activity against a broad spectrum of DNA viruses, including HSV-1 and 2, VZV, thymidine kinase-deficient (TK^-) mutants of herpes simplex HCMV, phocid herpesvirus type 1 (seal herpesvirus, SeHV), the simian herpesvirus platyrrhinae (HVP), suid herpesvirus type 1 (SHV-1, or pseudorabies virus or Aujeszky's disease virus), bovid herpesvirus type 1 (infectious bovine rhinotracheitis virus, BHV-1), equid herpesviruse type 1 (equine abortion virus, EHV-1), African swine fever (ASF) virus, vaccinia virus; and human adenoviruses, and retroviruses such as murine sarcoma virus (MSV). It is also reported that, in mice and rabbits in vivo, the compound is effective against both local and systemic infections with herpes simplex virus type 1, including herpetic keratitis caused by a TK^- mutant which is resistant to the classical anti-herpes drugs.

European Patent Application 205,826, to De Clercq, et al, published Dec. 30, 1986, discloses that HPMPA analogs are active against Moloney mouse sarcoma virus, and are expected to be effective against retroviruses in general. Reist and Sturm in PCT/U.S. 84/00737, published December 6, 1984 disclosed new phosphonic acid analogs of nucleoside phosphates which are useful as antivirals for incorporation into viral DNA.

Adenine phosphonic acid analogs and their synthesis are disclosed in the United Kingdom Patent application of Holy, et al., GB 2,134,907A, published on August 22, 1984, and it's related United States Patent, No. 4,659,825. A preferred example of one of these compounds, is known as (S)-9-((3-hydroxy-2-phosphonylmethoxy)propyl)adenine (HPMPA). HPMPA was disclosed by E. DeClercq, et al., in Nature, 323: 464-467, (1986), in Antiviral Research, 8: 261-272, (1987), and earlier by A. Holy, et al., Nucleic Acids Research, Symposium Series No. 14: 277-278, (1984).

Phosphonylmethoxyalkylpurine analogs have also been evaluated for their antitumor activity in murine tumor models. HPMPA, PMEA, and PMEG were found to be active against intraperitoneal P388 leukemia. PMEG was also found to be active against B16 melanoma. Rose, et al, J. of the Nat. Cancer Inst., Vol. 82, No. 6 (1990).

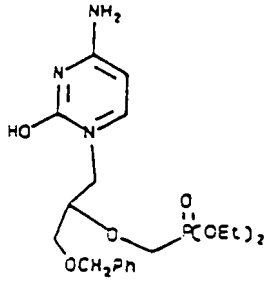
A problem with nucleotides and other ionic organophosphate esters is their inability to traverse biological membranes. Liebman, et al, J. Biol. Chem., 216: 823 (1955); Roll, et al, J. Biol. Chem., 220: 439

(1956). These compounds must, therefore, be given parenterally in order to achieve adequate serum levels to exert an antiviral effect.

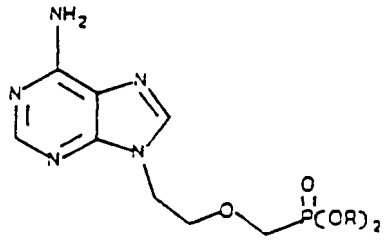
Parenteral treatment is highly undesirable, especially with HIV infected patients. With HIV infected patients oral treatment is preferred since (i) HIV infected patients ~~are very ill and need to be on~~ chronic chemotherapy programs to maintain their health; (ii) the risk of using needle stick and presence of blood is high for health workers; (iii) disposal of infected needles is problem; and (iv) the need for long-term maintenance therapy.

The inventors of this invention have carried out studies in order to circumvent the above-mentioned problem. The present application, thus, relates to the preparation and use of a number of oral prodrugs of phosphonate nucleotide analogs.

In J. Med. Chem, 32:1457-1463 (1989), Bronson et al., disclose the synthesis of HPMPC wherein the following compound is disclosed as an intermediate

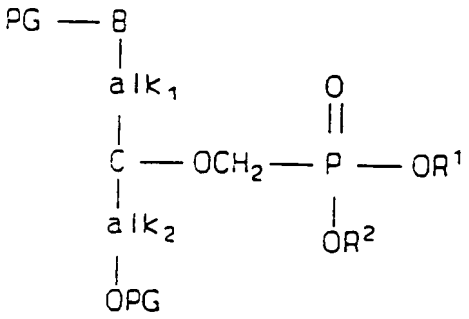


In Nucleotide Analogs as Antiviral Agents, ACS Symposium Series 401, J.C. Martin, Ed., p. 72, American Chemical Society, Washington, D.C. (1989), Bronson et al., disclose the synthesis of phosphonylmethoxy ether derivatives wherein the following compound was disclosed as an intermediate



wherein R is ethyl or isopropyl.

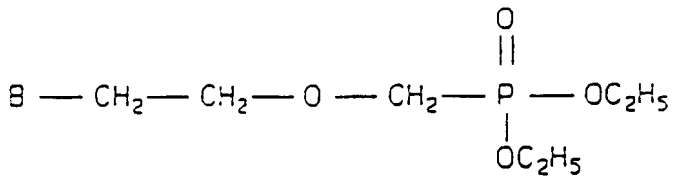
European Patent Application EP-270,885 of Webb, et al., published June 15, 1988 discloses a process for the preparation of purin-9-ylalkylenoxymethyl phosphonic acids, wherein several intermediates are produced in the practice of the process. One such intermediate is dialkylphosphonylmethyl which has the general structural formula



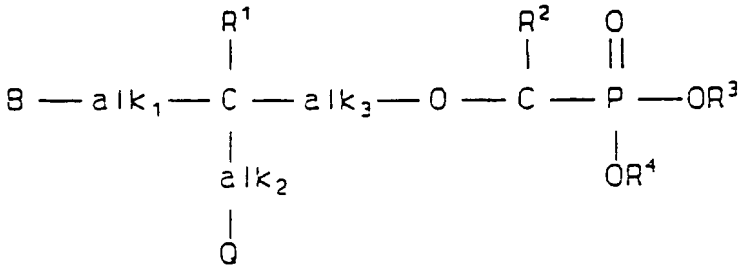
wherein R^1 and R^2, independently, are selected from C_{1-6} alkyl.

European Patent Application EP 253,412 of Holy, et al., published January 20, 1988, discloses the

preparation of a series of N-phosphonylmetnoxyalkyl derivatives of pyrimidine and purine bases exhibiting antiviral activity, wherein in the practice of the process, several intermediates are produced. One such intermediate has the general structural formula



European Patent Application EP-269,947 of R. R. Webb, II, et al., published on June 8, 1988, discloses a series antiviral agents which are phosphonomethoxyalkylene purine and pyrimidine derivatives having the following general structure

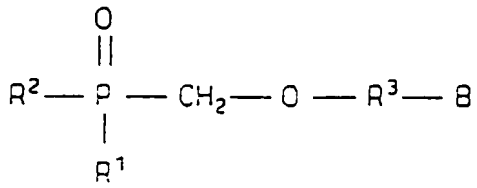


wherein R^3 and R^4 are independently selected from hydrogen, C_{1-16} alkyl, phenyl and phenyl-C_{1-4}-alkylene.

The art compounds are generally distinguished from the compounds of the instant invention by the nature of the groups attached to the phosphorous atom. There is no disclosure or suggestion in the above references, or combination thereof, which would make obvious the use of a suitably protected phosphonate derivative prodrug for oral use.

This invention relates novel prodrugs of phosphonate nucleotide analogs which exhibit antitumor activity and a broad spectrum of antiviral activity and some of which may be used orally.

The compounds of the instant invention comprise a diester-phosphonate link to nucleoside analogs of pyrimidine and purine bases. More particularly, it relates to compounds of the general structural formula as shown in Formula I



FORMULA I

wherein

B represents adenine (A), cytosine (C), guanine (G), thymine (T), Uracil (U), 2,6-diamino purine (DAP), hypoxanthine (Hx), or Z;

R^1 and R^2 are identical or different and independently of one another are each OR^4, NH_2, NHR^5, or N-$(R^5)_2$; in some cases, R^1 and R^2 are linked with each other to form a cyclic group, in other cases, R^1 or R^2 is linked to R^3 to form a cyclic group;

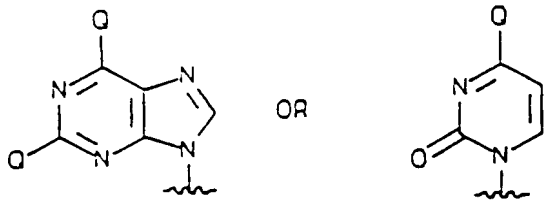
R^3 represents C_1 - C_{20} alkyl which may be substituted or unsubstituted by substituents independently selected from the group consisting of hydroxy, oxygen, nitrogen and halogen; when R^3 is $CH(CH_2OR^6)CH_2$, R^1 and R^2 each independently represent OH, and R^6 is a hydrolyzable ester group;

R^4 represents a physiologically hydrolyzable ester group such as $CH_2C(O)NR^5{}_2$, $CH_2C(O)OR^5$, $CH_2OC(O)R^5$, $CH(R^5)OC(O)R^5$ (R, S, or RS stereochemistry), $CH_2C(R^5)_2CH_2OH$, or CH_2OR^5; R^4 may also be $R^{5'}$ provided that R^4 and $R^{5'}$ are not simultaneously alkyl;

R^5 represents C_1 - C_{20} alkyl, aryl or aryl-alkyl which may be substituted or unsubstituted by substituents independently selected from the group consisting of hydroxy, oxygen, nitrogen and halogen;

$R^{5'}$ represents C_4 - C_{20} alkyl, aryl or aryl-alkyl which may be substituted or unsubstituted by substituents independently selected from the group consisting of hydroxy, oxygen, nitrogen and halogen; and

Z is independently chosen from



Q is independently chosen from H, Cl, NHR^5, $NR^5{}_2$, $NHC(O)R^5$, $N(C(O)R^5)_2$, OH or $NCHN(R^5)_2$.

Included within the scope of the invention are the pharmaceutically acceptable acid addition salts, the metal salts and the solvate of the compounds of Formula I which may exist in various tautomeric forms.

In one aspect, the application relates to a process for the preparation of the compounds of Formula I.

In another aspect, the application relates to the use the compounds of Formula I as a method for the treatment of viral infections in a mammal, which comprises administering an effective non-toxic dose of at least one compound of Formula I.

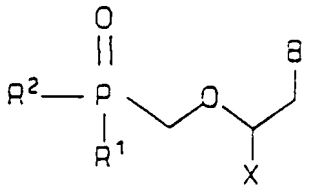
Another aspect of the application relates to the use of the compounds of Formula I as a method for inhibiting growth of a tumor in a mammal bearing a tumor which comprises administering an effective non-toxic dose of at least one compound of Formula I.

The compounds of Formula I are prodrugs of phosphonate nucleotides and have the same utility as the known or parent nucleotide analog. Thus the compounds of Formula I are useful as antiviral and antitumor agents.

The novel compounds of the present invention provide marked advantages over known nucleotides or analogs thereof in that these novel compounds are orally active.

The most preferred compounds of the invention are listed below, and experimental details for their preparation and characterization follow. Those which are not shown by specific example are readily prepared by analagous procedures.

A preferred example of the compounds of the instant invention are the compounds having the general structural formula as shown in Formula (II):



FORMULA II

wherein

B, R^1 and R^2 are as described in Formula I, provided that when Q is $NCHN(R^5)_2$, then R^5 is not CH_3;

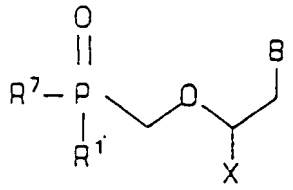
X represents hydrogen, methyl, CH_2OR^6 (R;S; or RS stereochemistry), hydroxymethyl or substituted or unsubstituted lower alkyl; when X is CH_2OR^6, R^1 and R^2, may additionally be independently chosen from OH; and

R^6 is a hydrolyzable group;

provided that when X is CH_2OR^6, R^6 is not CH_2Ph, and R^1 and R^2 are not both ethoxy; further, when R^1 is methoxy and R^2 is hydrogen, R^6 is not methyl; and further provided that when R^1 is methoxy and R^2 is

hydrogen, R^6 is not octyl.

Another preferred example of the compounds of the instant invention are the compounds having the general structural formula as shown in Formula (III):



FORMULA III

wherein

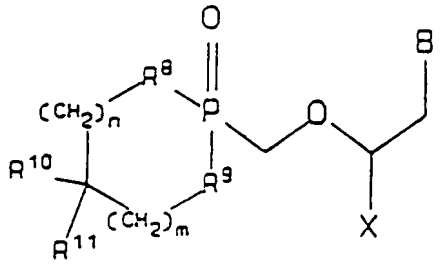
B, and R^1 are as previously described in Formula I;

X is as described in Formula II;

R^7 represents OH, NH_2, NHR^5, or $NR^5{}_2$; and

R^5 is as described in Formula I.

Still another preferred example of the compounds of the instant invention are the compounds having the general structural formula as shown in Formula (IV):



FORMULA IV

wherein

R^8 and R^9 are identical or different and independently of one another are each NR^{12}, or oxygen;

R^{10} and R^{11} are identical or different and independently of one another are each hydrogen, or R^5;

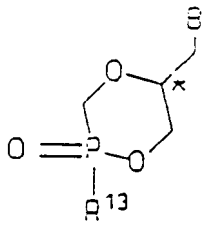
R^{12} represents hydrogen or a lower alkyl;

m and n are identical or different and independently of one another are each 0 or 1;

B and R^5 are as described in Formula I; and

X is as described in Formula II.

Yet another preferred example of the compounds of the instant invention are the compounds having the general structural formula as shown in Formula V



* stereochemistry is R, S, or RS

FORMULA V

wherein

R^{13} represents OR^4, NHR^5, NR^5_2, or OH, provided that R^{13} is not OH when B is A or C; and

B, R^4 and R^5 are as described in Formula I.

The term "C_1 to C_{20} alkyl" as used herein and in the claims (unless the context indicates otherwise) means saturated or unsaturated, branched or straight chain hydrocarbon group having 1 to 20 carbon atoms such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, etc. Unless otherwise specified in the particular instance, the term "substituted or unsubstituted" as used herein and in the claims is intended to mean hydrocarbon group wherein an atom, element or group is regarded as having replaced a hydrogen atom, said substituted alkyl groups are preferably substituted with a member selected from the group consisting of hydroxy, oxygen, nitrogen and halogen.

The term "prodrug" as used herein and in the claims (unless the context indicates otherwise) denotes a derivative of an active drug which is converted after administration back to the active drug. More particularly, it refers to derivatives of nucleotide phosphonates antiviral drugs which are capable of undergoing hydrolysis of the ester moiety or oxidative cleavage of the ester or amide moiety so as to release active, free drug. The physiologically hydrolyzable groups serve as prodrugs by being hydrolyzed in the body to yield the parent drug per se, and thus, the prodrugs of the present invention are preferably administered orally.

Synthesis of the phosphonate nucleotide analogs

The phosphonate nucleotide analogs are known compounds and therefore, the compounds as such and their chemical synthesis are not a part of the present invention. The synthesis of a number of phosphonate nucleotide analogs have been described in the literature.

For example, the synthesis of the phosphonates PMEA is disclosed in Holy and Rosenberg,Collect. Czech. Chem. Commun., 52:2801, (1987), and Bronson, et al, Nucleotide Analogues as Antiviral Agents, ACS Symposium Series 401, J.C. Martin, Ed., p. 72, American Chemical Society, Washington, D.C. (1989).

Bronson, et al, J. Med. Chem., 32: 1457-1463 (1989) discloses the preparation of HPMPC from (R)-2,3-O-isopropylideneglycerol.

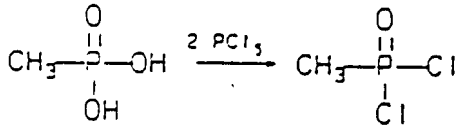
European Patent Application 253,412, published January 20, 1988 to Holy, et al, discloses methods for the preparation of PME and HPMP analogs of pyrimidine and purine bases.

Recently Holy et al Collect. Czech. Chem. Commun., 54: 2190-2210 (1989), described the preparation of N-(2-phosphonylmethoxy-ethyl) ("PME") analogs of purine and pyrimidine bases, as analogs of the antiviral 9-(2-phosphonylmethoxyethyl)adenine ("PMEA). The synthesis consists of alkylation of alkali metal salts of heterocyclic bases or their N-or O-substituted analogs with diethyl 2-p-toluenesulfonyloxyethyoxymethylphosphonate, 2-chloroethyoxymethylphosphonate, or 2-bromoethyoxymethyl-phosphonate. The obtained N-(2-diethyoxyphosphonylmethoxyethyl) analogs of heterocyclic bases were treated with bromotrimethylsilane to give phosphonic acids. The phosphonic acids were prepared from pyrimidines (uracil, cytosine and their 5-methyl analogs), purines (adenine and its N^6 and C(2)-substituted analogs, hypoxanthine, guanine, 6-hydrazinopurine and 6-methylthiopurine etc.) and their analogs (3-deazaadenine etc.).

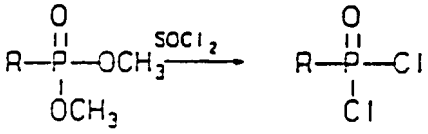
The synthesis of HPMPA is disclosed in Holy, Rosenberg, and Dvorakova, Collect. Czech. Chem. Commun. 54:2190 (1989).

Synthesis of dialkyl phosphonates

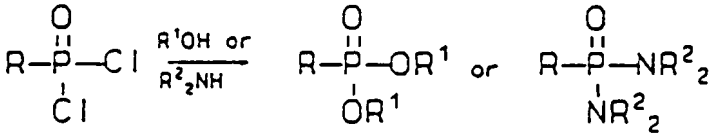
Quast, et al, Synthesis 490 (1974), has shown that dichlorophosphonates can be prepared by reacting phosphonates with PCl_5:



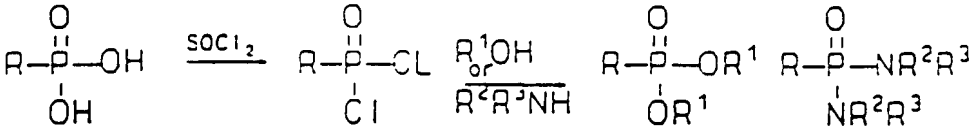
Moedritzer, K. CA 82, 86340, has shown that dichlorophosphonates can be prepared by reacting dimethylphosphonates with thionyl chloride.



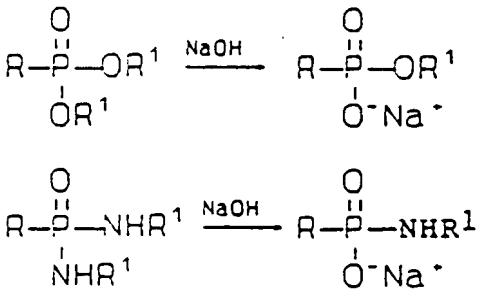
Stowell, et al, (Tetrahedron Lett., 3261, (1990)) has shown that dichlorophosphonates can be reacted with alcohols or amines to give dialkylesters or dialkylamides:



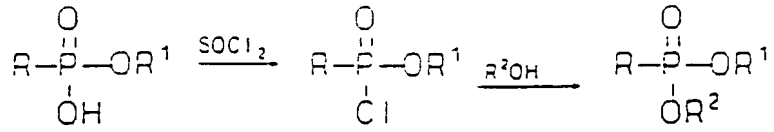
The substituted phosphonates of the present invention were prepared by several methods: 1) Reaction of the phosphonate with thionyl chloride to give the dichlorophosphonate which was reacted further to give the disubstituted phosphonate:



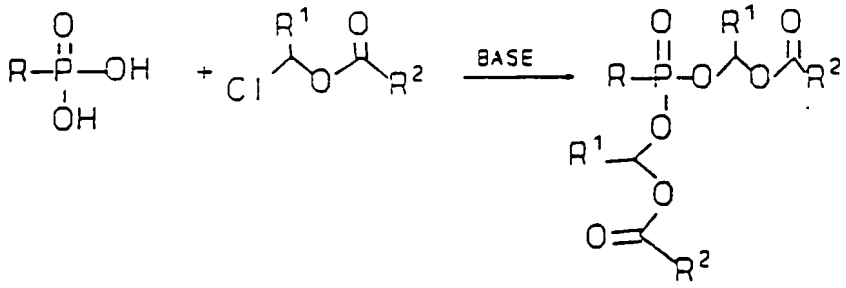
2) Mono substituted phosphonates were obtained by the basic hydrolysis of the disubstituted phosphonate:



3) The monosubstituted phosphonates were chlorinated as before and reacted with a different alcohol or amine to give variably substituted phosphonates:



4) Diacyloxyalkyl phosphonates were obtained by reaction of the unsubstituted phosphonate with a substituted chloromethyl ether:



PROTOCOL FOR DETERMINING ORAL BIOAVAILABILITY OF PRODRUGS

Groups of rats, 3 rats per group were given a single iv dose of 30 mg/kg of PMEA or a single oral dose of 30 mg-equiv/kg of PMEA or PMEA prodrug. Urine was collected in 0-24 hr and 24-48 hr intervals and analyzed for concentration of PMEA. The bioavailability of PMEA based on urinary excretion data and the bioavailability of PMEA when given as a prodrug was determined. The results are summarized below:

ORAL BIOAVAILABILITY OF SELECTED PMEA PRODRUGS IN RATS	
COMPOUND OF EXAMPLE NO.	ABSOLUTE BIOAVAILABILITY
1 (PMEA)	7.8
9	17.0
12	15.4
13	14.6
14	34.9**
15	6.5
16	14.2
22	16.2
34	14.0
35	11.1

**DETECTED AS THE MONOETHYL ESTER

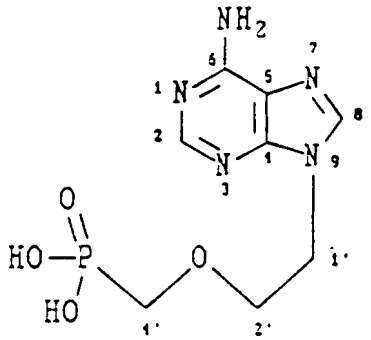
IN VITRO ACTIVITY OF SELECTED PMEA PRODRUGS AGAINST HSV-2 (G STRAIN)		
COMPOUND OF EXAMPLE NO.	ID_{50}(μg/mL)[a]	TOXICITY(μg/mL)
1 (PMEA)	39	>166
9	0.28	100
12	0.17	100
13	<0.1	100
14	3.3	100
15	8.1	100
16	>100	100
22	110	>166
34	42	>166
35	34	>166

[a]DOSE WHICH GIVES A 50% REDUCTION OF PLACQUE FORMATION

The compounds of Formula I may be formulated for oral or parenteral use in a conventional manner using known pharmaceutical carriers and excipients, and they may be presented in unit dosage form or in multiple dose containers. The compositions may be in the form of tablets, capsules, solutions, suspensions or emulsions. These compounds may also be formulated as suppositories utilizing conventional suppository bases such as cocoa butter or other fatty materials. The compounds may, if desired, be administered in combination with other antiviral antibiotics.

When provided in unit dosage forms, the compositions may contain from about 0.1 to about 100 mg/kg/dose of the active ingredient of Formula I. The dosage of the compounds of Formula I is dependent on such factors as the weight and age of the patient, as well as the particular nature and severity of the disease, and within the discretion of the physician. The dosage for adult human treatment may vary depending on the frequency and route of administration.

The following examples are intended for illustrative purpose only and are not to be construed as limiting the invention in sphere or scope. All temperatures are understood to be in degrees in C when not specified. The nuclear magnetic resonance (NMR) spectral characteristics refer to chemical shifts (δ) expressed in parts per million (ppm) versus tetramethylsilane (TMS) as reference standard. Except where otherwise noted, ^1H spectra were recorded at 300 MHz and ^{13}C spectra were recorded at 75 MHz. The relative area reported for the various shifts in the proton NMR spectral data corresponds to the number of hydrogen atoms of a particular functional type in the molecule. NMR assignments are based on the numbering system shown below:



The nature of the shifts as to multiplicity is reported as broad singlets (bs), singlets (s), multiplet (m), doublet (d), doublet of doublets (dd), triplet (t), or quartet (q). Coupling constants are given in hertz. When not specified, abbreviations employed are standard American Chemical Society (ACS) abbreviations as entered on the ACS Style Guide. The infrared (IR) spectral descriptions include only absorption wave numbers (cm^{-1}) having functional group identification value. All compounds gave satisfactory elemental analyses, or high resolution mass spectrometry (HRMS).

I. GENERAL EXPERIMENTAL METHODS FOR COMPOUNDS LISTED IN TABLE I:

The compounds listed in in Table I were synthesized by the corresponding method given at the end of

the table. The reaction time, temperature and yield are given in Table I. The structure of the examples corresponds to either Figure 1 or Figure 2 given at the top of Table I. Spectral data for all compounds are given in the Examples which follow.

TABLE I. STRUCTURES AND EXPERIMENTAL DATA FOR PMEA PRODRUGS

STRUCTURE					EXPERIMENTAL			
Example No.	Fig	R1	R2	R3	Method	Temp°C	Time(h)	Yield %
2	1	iPrO	=R¹	NH_2	e			
3	1	PhO	CH_3O	NH_2	e			
4	1	iPrO	HO	OH	e			

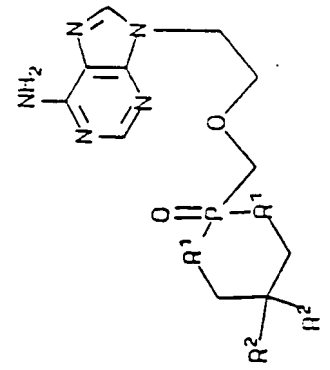


FIGURE 2

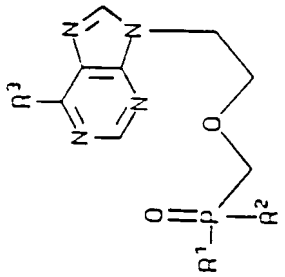


FIGURE 1

STRUCTURE					EXPERIMENTAL		
Example No.	Fig	R1	R2	R3	Method	Temp°C	Time(h)	Yield %
5	1	iPrO	=R^1	Cl	e			
6	1	iPrO	=R^1	H	e			
9	1	t-BuC(O)OCH_2O	=R^1	NH_2	e	-	-	-
10	1	t-BuC(O)OCH_2O	iPrO	NH_2	e			
11	1	$(CH_3)_3N(+)(CH_2)_2O$	O^-	NH_2	e	-	-	-
12	1	EtC(O)OCH_2O	=R^1	NH_2	e			
13	1	iPrC(O)OCH_2O	=R^1	NH_2	e			
14	1	tBuC(O)OCH_2O	CH_3CH_2O	NH_2	e			
15	1	tBuC(O)OCH_2O	OH	NH_2	e			
16	1	iPrO	PhO	NH_2	e			

Example No.	Fig	R1	R2	R3	EXPERIMENTAL			
					Method	Temp°C	Time(h)	Yield %
17	1	t-BuC(O)OCH_2O	$Et_2NC(O)CH_2O$	NH_2	e			
18	2	O	H	NH_2	C[b]	22	16	
19	1	Et_2N	$=R^1$	NH_2	C	22	16	18
20	1	iPrO	O^-	NH_2	B	60	24	75
21	2	O	CH_3	NH_2	C	40	24	56
22	1	$HO(CH_2)_3O$	O^-	NH_2	B	60	2	50
23	1	$CH_3(CH_2)_7O$	HO	NH_2	E	70	16	29
24	1	CH_3O	$=R^1$	NH_2	A	65	4	47
25	1	CH_3O	O^-	NH_2	B	60	2	78
26	1	$H_2NCH_2C(CH_3)_2CH_2NH-$	HO	NH_2	B	60	1.5	61

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STRUCTURE					EXPERIMENTAL			
Example No.	Fig	R1	R2	R3	Method	Temp°C	Time(h)	Yield %
27	1	$HOCH_2C(CH_3)_2CH_2O$	HO	NH_2	D	60	1.5	80
28	2	NH	CH_3	NH_2	C	40	24	46
29	2	NCH_3	H	NH_2	F	82	24	27
30	1	$Et_2NC(O)CH_2O$	O	NH_2	F;D[a,d]	0;22	20;0.3	19
31	1	$HOC(O)CH_2O$	HO	NH_2	D	22	0.1	66
32	1	$BuOC(O)CH_2O$	$=R^1$	NH_2	F	82	1	44
33	1	$EtOC(O)CH_2O$	$=R^1$	NH_2	F	82	2	51
34	1	PhO	O	NH_2	D	22	1	76
35	1	PhO	$=R^1$	NH_2	F	22	20	38
36	1	$iPr_2NC(O)CH_2O$	O	NH_2	F,D[a,d]	22;22	0.8;0.3	8

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STRUCTURE					EXPERIMENTAL			
Example No.	Fig	R1	R2	R3	Method	Temp°C	Time(h)	Yield %
37	1	pNO_2PhCH_2O	$=R^1$	NH_2	F	82	1	15
38	1	pNO_2PhCH_2O	O^-	NH_2	D	60	20	78
39	1	CCl_3CH_2O	$=R^1$	NH_2	F	82	20	44
40	1	CCl_3CH_2O	HO	NH_2	D	60	1	69
41	1	$PhC(O)OCH_2O$	$=R^1$	NH_2	e	22	20	9
42	1	pCF_3PhCH_2O	$=R^1$	NH_2	F	82	3	15
43	1	$HOCH_2CF_2CH_2O$	HO	NH_2	F;D[a,d]	82;22	1;1	18
44	1	pCF_3PhCH_2O	HO	NH_2	D	60	20	82
45	1	$CH_3(CH_2)_3NH$	$=R^1$	NH_2	F	82	20	27
46	1	$(CH_3)_2CHCH_2O$	$=R^1$	NH_2	A	60	3	75

STRUCTURE				EXPERIMENTAL			
Example No.	Fig	R1	R2	R3	Method	Temp°C	Time(h)	Yield %
47	1	$(CH_3)_2CH(CH_2)_2O$	$=R^1$	NH_2	A	80	1.5	77

[a] The crude product obtained from method F was employed directly in method D. Temperature and time are given for methods F and D, respectively.

[b] The impure product obtained from column chromatography was recrystallized from 25% MeOH/CH_3CN.

[c] The impure product obtained from column chromatography was recrystallized from CH_3CN.

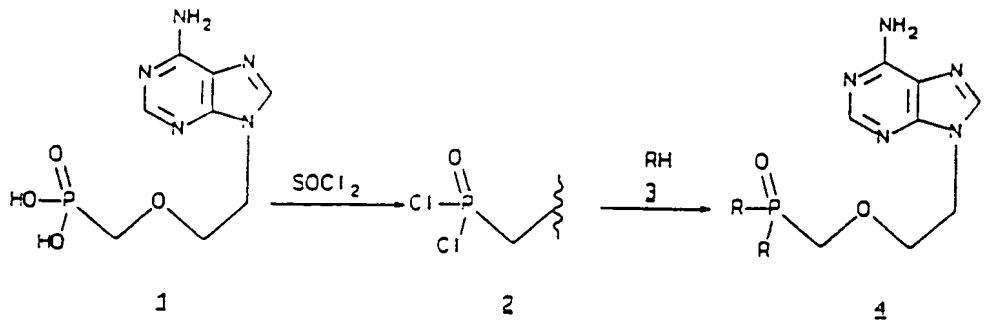
[d] See detailed experimental section for synthesis of hydroxyacetamides and difluoroalcohol.

[e] Where no method is given, see detailed experimental section for specific examples.

METHOD OF SYNTHESIS FOR THE COMPOUNDS OF TABLE 1

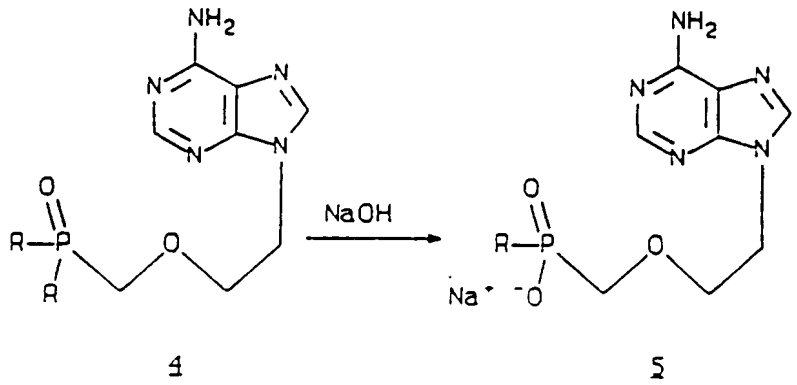
A: A suspension of 1.00 g (3.66 mmol) of PMEA (1) in 50 mL of thionyl chloride was refluxed for 1 h (see eq. 1). The homogeneous, orange-red solution was cooled and the solvents were removed in vacuo to afford crude dichlorophosphonate 2. The dichloride was taken up in alcohol or amine 3 and stirred at the

temperature and the time given in Table I. After cooling the reaction to room temperature the solvents were removed in vacuo. The residue was purified on a 30 mm flash chromatography column, eluting with 10% MeOH/CH_2Cl_2 to afford 4. (See eq. I)



(eq. 1)

B: An aqueous suspension of 4 was treated with 4 equivalents of NaOH for the time and temperature given in Table I (see eq. 2). The mixture was cooled to room temperature and acidified until pH 8. The majority of the solvent was evaporated and the residue was purified on a C-18 silica gel column, eluting with a gradient of 0-25% MeOH/H_2O. The fractions containing the product were combined and evaporated to give 5. (See eq. 2)



(eq. 2)

C: This reaction was performed similarly to method A, except crude dichlorophosphonate 2 was suspended in 30 mL of methylene chloride before adding alcohol or amine 3 (see equation 1).

D: This reaction was performed similarly to method B, except after cooling to room temperature, the reaction was acidified to pH 1.5. (See equation 2).

E: This reaction was run similarly to method B, except after cooling to room temperature the reaction was suspended in 20 mL of water. The mixture was acidified until pH approximately 3-4. The resulting solid was collected and washed with water. The filtrate was cooled to 0 °C and the resulting solid was collected and washed with cold water. The solids were combined and dried overnight at 0.005 mm to afford 106 mg (0.23 mmol) of monooctyl-PMEA.

F: This reaction was performed similarly to method A, except crude dichlorophosphonate 2 was suspended in 30 mL of acetonitrile before adding alcohol or amine 3 (see equation 1).

SPECIFIC EXPERIMENTAL METHODS FOR COMPOUNDS LISTED IN TABLE I.

EXAMPLE 1

Synthesis of 9-(2-Phosphonylmethoxy)ethyladenine (PMEA).

A solution of PMEA diisopropyl ester (75.5 g, 0.21 mol) in 800 mL of anhydrous acetonitrile was treated with bromotrimethylsilane (258 g, 1.69 mol). The resulting clear, yellow solution was stirred at room temperature under argon for about 16 hours. The reaction mixture was concentrated in vacuo and the yellow residue was placed under high vacuum for about 5 hours. 400 mL of water was added next, causing immediate formation of a white precipitate. 500 mL of acetone was added and the pale yellow slurry was stirred at room temperature for about 14 hours. The solid was collected by filtration, washing twice with 150 mL of acetone and once with 150 mL of anhydrous ether. An additional portion of solid was collected from the filtrate to provide a total of 55.0 g (90%) of PMEA as an off-white crystalline solid.
m.p.> 250°C; UV_{max} (H_2O) 208 nm (ϵ = 19,600) 260 nm (ϵ = 14,100); UV_{max} (0.1 N HCl) 210 nm (ϵ = 19,000) 260NM (ϵ = 13,700); UV_{max} (0.1 N NaOH) 216 nm (ϵ = 9,600) 262 nm (ϵ = 14,500); ^{1}H NMR (DMSO-d_6) δ 8.14 (s, 1 H), 8.13 (s, 1 H), 7.27 (br s, 2 H, NH_2), 4.32 (t, J = 5, 2 H, H-1'), 3.87 (t, J = 5, 2H, H-2'), 3.59 (d, J = 9, 2H, H-4'); ^{13}C NMR (DMSO-d_6) δ 151.10 (c-6), 148.70 (C-2), 146.28 (C-4), 143.80 (C-8), 118.05 (C-5), 69.94 (d, J = 10, C-2'), 66.27 (d, J = 160, C-4'), 43.15 (C-1').

EXAMPLE 2

Synthesis of PMEA, diisopropyl ester

A slurry of adenine (21.2 g, 157 mmol), 2-[(diisopropylphosphonyl)methoxy]ethyl methanesulfonate (50.0 g, 157 mmol, prepared according to the procedure described by J.J. Bronson et al, in J. Med. Chem., 32: 1457, (1989)), and cesium carbonate (56.0 g, 173 mmol) in 160 mL of anhydrous DMF was heated to 120°C in a 3-necked, 500-mL, round-bottomed flask equipped with a mechanical stirrer and argon inlet adapter. The reaction mixture was stirred at 120°C for about 5 hours and then was allowed to cool to room temperature. Insoluble material was removed by filtration and the filtrate was concentrated in vacuo to give 66 g of a yellow solid. Purification by column chromatography on silica gel (10:1, elute with 3% to 5% to 7% MeOH/CH_2Cl_2) provided 33 g of an off-white solid. Recrystallization from ethyl acetate provided 30.1 g (54%) of PMEA, diisopropyl ester as a white solid.
Mp 136-138°C; UV_{max} (MeOH) 262 nm (ϵ = 14,360); ^{1}H NMR (DMSO-d_6) δ 8.15 (s, 1H), 8.09 (s, 1H), 7.21 (br s, exch, 2H, NH_2), 4.50 (apparent octet, J = 6.5 H, 2H, 2POCH), 4.34 (t, J = 5 H, 2H, NCH_2), 3.91 (t, J = 5 Hz, 2H, CH_2OCH_2P), 3.79 (d, J = 8 Hz, 2H, OCH_2P), 1.18 (d, J = 6.5 H, 6H, $POCH(CH_3)_2$], and 1.13 (d, J = 6.5 Hz, 6H, $POCH(CH_3)_2$]); ^{13}C NMR (DMSO-d_6) δ 155.86 (C-6), 152.23 (C-2), 149.46 (C-4), 140.90 (C-8), 118.57 (C-5), 70.22 (d, J = 10 Hz, POCH), 70.05 (d, J = 12 Hz, (CH_2OCH_2P), 64.50 (d, J = 165 Hz, OCH_2P), 42.35 (NCH_2), 23.61 [d, J = 7 H, $POCH(CH_3)_2$], and 23.52 [d, J = 7 Hz, $POCH(CH_3)_2$]; mass spectrum (methane DCI), m/e (rel intensity) 358 (MH^+, 100), 344 (10), 316 (10).

Anal. Calc. for $C_{14}H_{24}N_5O_4P$:	C, 47.06;	H, 6.77;	N, 19.60.
Found:	C, 47.06;	H, 7.04;	N, 19.65.

EXAMPLE 3

Synthesis of PMEA, (monomethyl, monophenyl) ester

The crude residue from the reaction of phenol with dichlorophosphonyl-PMEA (see General Method F) was purified on a flash chromatography column, eluting with 10% MeOH/CH_2Cl_2. Two compounds were obtained. PMEA, diphenyl ester eluted first (38%), followed by PMEA, monomethyl, monophenyl ester (16%).
Mp 70-72°C. ^{1}H NMR (d_6-DMSO) 8.13 (1H, s, H-8), 8.08 (1H, s, H-2), 7.32 (2H, t, J = 8, ArH), 7.20 (2H, s, NH_2), 7.17 (1H, t, J = 7, ArH), 7.00 (2H, d, J = 8.5, ArH), 4.34 (2H, t, J = 5, H-1'), 4.02 (2H, dd, J = 8.3, H-4'), 3.91 (2H, t, J = 5, H-2'), 3.67 (3H, d, J = 11, CH_3). ^{13}C NMR (d_6-DMSO; 90 MHz), 156.20 (C-6), 152.84 (C-2), 150.07 (ArC, d, J = 8), 149.85 (C-4), 141.79 (C-8), 130.31, 125.64, 120.77 (ArC), 118.84 (C-5), 70.87 (C-2', d,

J = 11), 63.53 (C-4', d, J = 163), 53.83 (CH_3, d, J = 8), 43.01 (C-1', IR (KBr) 3270, 3110, 1670, 1600, 1484. MS (FAB) 364 (M + H, 100).

Anal. Calcd for $C_{15}H_{18}N_5O_4P \cdot 0.16\ H_2O$:	C, 49.20;	H, 5.04;	N, 19.13.
Found:	C, 49.51;	H, 4.92;	N, 18.73.

EXAMPLE 4

Synthesis of 9-(2-Phosphonylmethoxy)ethylhypoxanthine (PMEHx), monoisopropyl ester.

A solution of 6-chloro-9-(2-phosphonylmethoxy) ethylpurine, diisopropyl ester (1g, 2.65 mmol) in 27 mL of 1 N NaOH was heated at reflux for 1 h, cooled to room temperature, acidified to pH 1 with 1 N HCl and concentrated in vacuo. The residue was purified by C-18 silica gel column chromatography, eluting with 20% MeOH/H_2O to afford 0.51 g (68%) of the title compound.
Mp 192-194 °C. ^1H NMR (d_6-DMSO) 12.27 (1H, br s, NH), 8.04, 8.02 (2H, 2s, H-2, H-8), 4.39 (1H, septet, J = 6, $CH(CH_3)_2$), 4.30 (2H, t, J = 5, H-1'), 3.85 (2H, t, J = 5, H-2'), 3.65 (2H, d, J = 8.5, H-4'), 1.10 (6H, d, J = 6, CH_3). ^{13}C NMR (D_2O) 157.57 (C = 0), 149.94, 149.72 (C-2, C-4), 143.02 (C-8), 119.94 (C-5), 72.09 ($CH(CH_3)_2$, d, J = 6), 71.70 (C-2', d, J = 13), 67.80 (C-4', d, J = 160), 47.05 (C-1'), 25.28 (CH_3, d, J = 4), IR (KBr) 3423, 2979, 1716, 1642, 1587, 1562. MS (FAB) 317 (M + H, 100).

Anal. Calcd for $C_{11}H_{17}N_4O_5P \cdot 0.4\ H_2O$:	C, 40.95;	H, 5.53;	N, 17.37.
Found:	C, 41.19;	H, 5.68;	N, 17.51.

EXAMPLE 5

Synthesis of 6-Chloro-9-(2-Phosphonylmethoxy) ethylpurine, diisopropyl ester.

To a rapidly stirred solution of 9.86 g (63.8 mmol) of 6-chloropurine in 350 mL of anhydrous DMF was added 1.91 g (63.8 mmol) of sodium hydride (80% in mineral oil). The heterogeneous mixture was heated at 95 °C for about 20 hours, cooled to room temperature and concentrated in vacuo. The residue was purified by silica gel chromatography, eluting with 5% MeOH/CH_2Cl_2 to give 4.53 g of the title compound.
^1H NMR (d_6-DMSO) 8.76 (1H, s, H-8), 8.63 (1H, s, H-2), 4.82 (2H, t, J = 5, H-1'), 4.42 (2H, septet, J = 6, $CH(CH_3)_2$, 3.93 (2H, t, J = 5, H-2'), 3.75 (2H, d, J = 8, H-4'), 1.11 (6H, d, J = 6, CH_3), 1.05 (6H, d, J = 6, CH_3). ^{13}C NMR (d_6-DMSO) 152.44 (C-6), 151.88 (C-2), 149.39 (C-4), 148.13 (C-8), 131.13 (C-5), 70.24 ($CH(CH_3)_2$, d, J = 6), 70.00 (C-2', d, J = 11), 64.64 (C-4', d, J = 165), 43.43 (C-1'), 23.65 (CH_3, d, J = 4.5), 23.47 (CH_3, d, J = 4.5). IR (KBr) 3459, 3077, 2982, 2936, 1564. MS (methane/DCI) 377 (M + H, 100).

Anal. Calcd for $C_{14}H_{22}N_4O_4ClP_1$:	C, 44.63;	H, 5.89;	N, 14.87.
Found:	C, 44.40;	H, 5.93;	N, 14.53.

EXAMPLE 6

Synthesis of 9-(2-phosphonylmethoxy)ethylpurine, diisopropyl ester.

A solution of 6-Chloro-9-(2-phosphonylmethoxy) ethylpurine, diisopropyl ester (0.94 g, 2.5 mmol) in 20 mL of ethanol/cyclohexene (1:1) was treated with 0.5 g of $Pd(OH)_2/C$. The reaction was stirred at reflux for about 20 hours, diluted with hot ethanol and flitered through celite. The filtrate was concentrated in vacuo and the residue was purified by flash column chromatography, eluting with 10% MeOH/CH_2Cl_2 to afford 0.49 g (58%) of the title purine as a clear yellow oil.
^1H NMR (d_6-DMSO) 9.14, 8.92, 8.55 (3H, 3s, H-2, H-6, H-8), 4.47 (2H, t, J = 5, H-1'), 4.42 (2H, septet, J = 6, $CH(CH_3)_2$), 3.94 (2H, t, J = 5, H-2'), 3.77 (2H, d, J = 8, H-4'), 1.12 (6H, d, J = 6, CH_3), 1.05 (6H, d, J = 6, CH_3). IR 3459, 2982, 2937, 1597, 1581, 1506. MS (methane/DCI) 343 (M + H, 100), 329 (12), 301 (50).

Anal. Calcd for $C_{14}H_{23}N_4O_4P \cdot 0.25\ H_2O$:	C, 48.50;	H, 6.83;	N, 16.16.
Found:	C, 48.55;	H, 6.71;	N, 15.88.

EXAMPLE 7

Synthesis of hydroxyacetamides necessary for preparation of Example 21 and Example 27.

(a) 2-hydroxy-N-N-diethylacetamide

A solution of 10.5 g (0.0702 mol) of 2-chloro-N-N- diethylacetamide in 35 mL of glacial acetic acid was refluxed for about 16 hours. The solvents were removed in vacuo, the last traces of acetic acid being azeotropically removed with toluene. The residue was dissolved in 125 mL of methanol and treated with 10.85 g (0.20 mol) of sodium methoxide. The reaction was stirred for about 3 hours and neutralized with Dowex 50X8-200 acidic ion exchange resin. The solvents were removed in vacuo and the residue was purified on a flash chromatography column, eluting with hexane/ethyl acetate 1:1 to give 6.75 g (73%) of 2-hydroxy-N-N-diethyl- acetamide.

(b) 2-hydroxy-N-N-diisopropylacetamide

To a solution of 44.5 g (0.44 mol) of N-N-diisopropyl amine in 125 mL of hexane cooled to -78 °C was added dropwise 17.6 mL (0.22 mol) of chloroacetyl chloride. After completion of the addition, the cooling bath was removed and stirring was continued for about 30 minutes. The isopropylammonium chloride was removed by filtration through celite and the filtrate was stripped to give 30.5 g (77%) of 2-chloro-N-N-diisopropylacetamide. Hydrolysis of this compound as described above afforded a 45% yield of 2-hydroxy-N-N-diisopropylacetamide.

EXAMPLE 8

Synthesis of the difluoroalcohol necessary for the preparation of Example 34.

(a) 2,2-Difluoro-3-hydroxy-propan-1-ol

A solution of 9.07 g (0.0521 mol) of 1,3-diacetyl acetone in 20 mL of DAST was stirred at 22 °C for 2 days, diluted with ethyl acetate, washed with saturated $NaHCO_3$ and water, then dried over Na_2SO_4 and concentrated to yield 9.54 g of 1,3-diacetyl-2,2-difluoropropane. The diacetyl-difluoropropane (7.53 g, 38.4 mmol) was dissolved in 300 mL of methanol and treated with 6.45 g (119 mmol) of sodium methoxide. After stirring at 22 °C for about 2.5 hours, the reaction was neutralized with Dowex 50X8-200 acidic ion exchange resin, filtered and stripped to give 3.7 g (86%) of the title compound.

EXAMPLE 9

Synthesis of PMEA, di(pivaloyloxymethyl ester)

To a rapidly stirred solution of 1.00 g (3.66 mmol) of PMEA in 15 ml of anhydrous DMF was added 2.08 g (7.32 mmol) of N,N'-dicyclohexyl-4-morpholine carboxamidine and 2.75 g (18.33 mmol) of chloromethyl pivalate. The heterogeneous mixture became homogeneous after about 15 minutes and was then allowed to stir at 22 °C for about 36 hours. The insolubles were filtered off and the filtrate was concentrated in vacuo. The residue was then partitioned between (50 ml) water and (50 ml) toluene, separated and the water layer was then extracted with (2 x 50 ml) toluene. The toluene layers were combined and concentrated in vacuo. The residue was purified by silica gel chromatography, eluting with 5% MeOH/CH_2Cl_2 to give 0.59 g (32%) of the title compound.

^1H NMR($CDCl_3$) 8.32(1H, s, H-8), 7.91(1H, s, H-2), 5.77(2H, s, NH_2), 5.63(4H, m, CH_2OP), 4.37(2H, t, J = 5.0, H-1'), 3.92 (2H,t,J = 5.0,H-2'), 3.82 (2H, d, J = 7.7, H-4'), 1.18(18H, s, CH_3). ^{13}C NMR ($CDCl_3$) 177.55(C = O), 156.23(C-6), 153.45(C-2), 150.48(C-4), 142.05(C-8), 119.85(C-5), 82.04 (CH_2OP,d,J = 6.0), 71.70(C-2', d, J = 9.8), 65.86(C-4', d, J = 167), 43.63(C-1'), 38.95(CC(= O), 27.11(CH_3). IR(KBr) 3366, 3178, 2976, 1754, 1660, 1600. MS(Isobutane/DCI) 502(M + H,100).

Anal. Calcd. for $C_{20}H_{32}N_5O_8P_1$:	C, 47.90;	H, 6.43;	N, 13.96.
Found:	C, 48.02;	H, 6.27;	N, 13.63.

EXAMPLE 10

Synthesis of PMEA, (mono isopropyl, mono pivaloyloxymethyl) ester

To a rapidly stirred solution of 200 mg (0.6 mmol) of monoisopropyl PMEA (example 11) in 5 ml of anhydrous DMF was added 0.83 ml (6.0 mmol) of Et_3N and 0.45 g (3.0 mmol) of chloromethylpivalate. The heterogeneous mixture became homogeneous after addition of Et_3N and was then allowed to stir at 22 °C for about 3 days. The mixture was concentrated in vacuo and the residue was purified by silica gel chromatography, eluting with 10% MeOH/CH_2Cl_2 to give 190 mg (74%) of the title compound.

^1H NMR($CDCl_3$) 8.30(1H, s, H-8), 7.91(1H, s, H-2), 5.94(2H, s, NH_2), 5.57(2H, d, J = 12.5, CH_2OP), 4.73 (1H, septet, J = 6.2, CH), 4.36(2H, t, J = 5.0, H-1'), 3.90(2H, t, J = 5.0, H-2'), 3.75(2H, d, J = 8.0, H-4', 1.25(6H, d, J = 6.2, CH_3), 1.17(9H, s, CH_3). ^{13}C NMR ($CDCl_3$) 177(C = 0), 155.51(C-6), 152.91(C-2), 149.8 (C-4), 141.43-(C-8), 119.36(C-5), 81.90(CH_2OP, d, J = 5.6), 72.18(CHOP, d, J = 7.0), 71.19(C-2', d, J = 10.0), 65.78(C-4', d, J = 167), 43.37 (C-1'), 38.68($(CH_3)_3C$), 26.84($(CH_3)_3C$), 23.92($\underline{C}H_3CH$, d, J = 7), 23.85($\underline{C}H_3CH$, d, J = 7). IR-(KBr) 3432, 1754, 1668, 1602. MS(FAB) 430($\overline{M}$ + H, 100).

Anal. Calcd. for $C_{17}H_{28}N_5O_9P_1 \cdot 0.50\ H_2O$:	C, 46.56;	H, 6.66;	N, 15.98.
Found:	C, 46.50;	H, 6.61;	N, 15.81.

EXAMPLE 11

Synthesis of PMEA, monocholine ester

A suspension of 2.00 g (7.33 mmol) of PMEA in 30 ml of thionyl chloride was refluxed for about 1 hour. The homogeneous, orange-red solution was cooled and the solvents were removed in vacuo to afford crude dichlorophosphonate. The dichloride was taken up in 40 ml of acetonitrile and then treated with 2.00 g (32.34 mmol) of anhydrous ethylene glycol at reflux for about 16 hours. After cooling to 22 °C, the solvents were removed in vacuo. The residue was purified by silica gel chromatography, eluting with MeOH/CH_2Cl_2/NH_4OH 30/70/1 to give 1.42 g (65%) of mono(chloroethyl)ester.

A suspension of 460 mg (1.37 mmol) of the above compound in 30 ml of MeOH was saturated with Me_3N gas at 0 °C. The reaction mixture was then sealed in a metal bomb and heated at 65 °C for about 2 days.

After cooling the reaction to 22 °C, the solvents were removed in vacuo and the residue was purified by C-18 chromatography, eluting with 15% MeOH/H_2O to give 270 mg (35% from PMEA) of the title compound.

^1H NMR(CD_3OD) 8.24(1H, s, H-8), 8.20(1H, s, H-2), 4.42(2H, t, J = 5.0, H-1'), 4.12(2H, CH_2CH_2OP), 3.89(2H, t, J = 5.0, H-2'), 3.64(2H,d,J = 9.0,H-4'), 3.47 (2H, m, CH_2OP), 3.14(9H, s, CH_3). ^{13}C NMR (CD_3OD) 157.55(C-6), 154.03(C-2), 151.02(C-4), 144.02(C-8), 120.15(C-5), 72.04(C-2'), 68.24(C-4',d, J = 159), 68.05 (CH_2OP), 60.10(CH_2CH_2OP,d,J = 4.9), 55.02(CH_3), 54.98(CH_3), 54.92(CH_3), 44.95(C-1'). IR(KBr) 3396, 1648, 1602, 1480. MS(FAB) 359(M + H,30).

Anal. Calcd. for $C_{13}H_{23}N_6O_4P_1 \cdot 2.5H_2O$:	C, 38.60;	H, 7.00;	N, 20.78.
Found:	C, 38.26;	H, 6.60;	N, 20.47.

EXAMPLE 12

Synthesis of PMEA, di-(propionyloxymethyl ester)

To a rapidly stirred solution of 1.00 g (3.66 mmol) of PMEA in 15 ml of anhydrous DMF was added 2.08

g (7.32 mmol) of N,N'-dicyclohexyl-4-morpholine carboxamidine and 2.23 g (18.3 mmol) of chloromethylpropionate. The heterogeneous mixture became homogeneous within 30 minutes and was then allowed to stir at 22°C for about 5 days. The insolubles were filtered off and the filtrate was concentrated in vacuo. The residue was purified twice by silica gel chromotography (200:1), eluting with 5%MeOH/CH_2Cl_2 to give 0.14g (9%) of the title compound.

^{1}H NMR($CDCl_3$) 8.29(1H, s, H-8), 7.88(1H, s, H-2), 5.65(2H, s, NH_2), 5.60(4H, m, CH_2OP), 4.35(2H, t, J=5.0, H-1'), 3.89(2H, t, J=5.0, H-2') 3.80(2H, d, J=7.8, H-4'), 2.34(4H, q, J=7.5, CH_3CH_2), 1.10 (6H, t, J=7.5, CH_3). IR(KBr) 3290, 3122, 1766, 1666, 1602. MS(FAB) 446(M+H, 100).

Anal. Calcd. for $C_{16}H_{24}N_5O_8P_1$:	C, 43.15;	H, 5.43;	N, 15.72.
Found:	C, 43.07;	H, 5.46;	N, 15.42.

EXAMPLE 13

Synthesis of PMEA, di-(isobutyrloxymethyl ester)

To a rapidly stirred solution of 1.00 g (3.66 mmol) of PMEA in 15 ml of anhydrous DMF was added 2.08 g (7.32 mmol) of N,N'-dicyclohexyl-4-morpholine carboxamidine and 2.48 g (18.3 mmol) of chloromethylisobutyrate. The heterogeneous mixture became homogeneous within 30 minutes and was then allowed to stir at 22°C for 5 days. The mixture was concentrated in vacuo, partitioned between (50 ml) water and (50 ml)toluene. The aqueous layer was extracted with (250 ml) toluene and the combined organic layer was concentrated in vacuo. The residue was purified by silica gel chromatography, eluting with 5% MeOH/CH_2Cl_2 to give 0.16 g (9%) of the title compound.

^{1}H NMR($CDCl_3$) 8.31(1H, s, H-8), 8.28(1H, s, H-2), 5.68(2H, s, NH_2), 5.59(4H, m, CH_2OP), 4.33(2H, t, J=5.0, H-1'), 3.88(2H, t, J=5.0, H-2'), 3.78(2H, d, J=7.7H, H-4'), 2.52(2H, apparent heptet, J=7.0, CH), 1.11(6H, d, J=7.0, CH_3). IR(KBr) 3360, 2980, 1758, 1660, 1602. MS(Isobutane/DCI) 474(M+H, 100).

Anal. Calcd. for $C_{18}H_{28}N_5O_8P_1 \cdot 0.65\ H_2O$:	C, 44.56;	H, 6.09;	N, 14.44.
Found:	C, 45.67;	H, 5.96;	N, 14.79.

EXAMPLE 14

Synthesis of PMEA, (mono ethyl, mono isobutyryloxymethyl) ester

To a rapidly stirred solution of 400 mg (1.33 mmol) of monoethyl PMEA in 15 ml of anhydrous DMF was added 2.00 ml (14.3 mmol) of Et_3N and 1.0 g (6.7 mmol) of chloromethylpivalate. The heterogeneous mixture became homogeneous after addition of Et_3N and was then allowed to stir at 22°C for 2 days. The mixture was concentrated in vacuo and the residue was purified by silica gel chromatography, eluting with 10% MeOH/CH_2Cl_2 to give 180 mg (33%) of the title compound.

^{1}H NMR($CDCl_3$) 8.32(1H, s, H-8), 7.92(1H, s, H-2), 5.74(2H, s, NH_2), 5.62(2H, m, OCH_2OP), 4.38 (2H, t, J=5.0, H-1'), 4.10(2H, m, CH_3CH_2OP), 3.92(2H, t, J=5.0, H-2'), 3.79(2H, d, J=8.0, H-4'), 1.27 (3H, t, J=7.0, CH_3CH_2), 1.18 (9H, s, $((CH_3)C)$. ^{13}C NMR ($CDCl_3$) 176.87(C=0), 155.40(C-6), 152.94(C-2), 149.8(C-4), 141.51(C-8), 119.7(C-5), 81.85(CH_2OP, d, J=6.2), 71.26(C-2', d, J=10.2), 65.46(C-4', d, J=167), 62.73-(CH_2CH_3, d, J=7.0), 43.49(C-1'), 38.70($(CH_3)_3C$), 26.84($(CH_3)_3C$), 16.27(CH_2CH_3, d, J=5.8), IR(KBr) 3288, 3120, 2982, 1752, 1666, 1600. MS(FAB) 416(M+H; 100).

Anal. Calcd. for $C_{16}H_{26}N_5O_6P_1 \cdot 0.5H_2O$:	C, 45.28;	H, 6.41;	N, 16.51.
Found:	C, 45.47;	H, 6.34;	N, 16.55.

EXAMPLE 15

Synthesis of PMEA, mono pivaloyloxymethyl ester

To a solution of sodium hydride(0.95 g, 60%, 31.7 mmol) and benzylalcohol (6.8 ml, 63.5 mmol) in anhydrous DMSO (50 ml) was added with stirring a solution of PMEA, diphenyl ester (3.4 g, 8 mmol, example 26) in DMSO(50 ml). The mixture was allowed to stir at 22 °C for 1 h and concentrated to a volume of approximately 25 ml. EtOAc (200 mL) was added and the precipitate was collected by vacuum filtration. The precipitate was purified by C-18 chromatogrophy, eluting with 20% MeOH/H_2O to give 2.09 g 68%) of PMEA, monobenzylester, sodium salt.

To 600 mg (1.56 mmoles) of the above compound in 14 ml of anhydrous DMF was added 2.16 ml (15.5 mmoles) of Et_3N and 1.44 g (9.61 mmol) of chloromethylpivalate. The mixture was allowed to stir at 22 °C for 2 days, concentrated in vacuo and the resulting residue was used crude in the following step.

To a stirred solution of the crude mixed ester (300 mg) in 17 ml of EtOH and 17 ml of H_2O was added 3.45 ml of cyclohexene and 0.225g of 20% $Pd(OH)_2/C$. The mixture was heated at reflux for 1h, concentrated in vacuo and the residue purified by C-18 chromatography, eluting with 100% H_2O to give 270 mg (31% from PMEA, diphenyl ester) of the title compound.

^1H NMR(d_6-DMSO) 8.09(2H, s, H-8, H-2), 7.17(2H, s, NH_2), 5.44(2H, m, CH_2OP), 4.26(2H, t, J = 5.0, H-1'), 3.83 (2H,t, J = 5.0, H-2'), 3.47(2H, d, J = 8.0, H-4'), 1.04(9H, s, CH_3). ^{13}C NMR (d_6-DMSO) 176.70(C = 0), 155.98(C-6), 152.39(C-2), 149.55(C-4), 141.30(C-8), 118.59(C-5), 83.14(CH_2OP), 69.89(C-2'), 64.5(C-4'), 42.84 (C-1'), 38.13 ($(CH_3)_3\underline{C}$) 26.69(CH_3). IR(KBr) 3360, 1742, 1648, 1602.

MS(FAB) 386(M-H, 100). HRMS:	
Calculated:	388.1386.
Found:	388.1377.

EXAMPLE 16

Synthesis of PMEA, (mono isopropyl, monophenyl) ester

A suspension of 0.75 g (2.1 mmol) of monophenyl PMEA in 20 ml of thionyl chloride was refluxed for 1 h. The homogeneous, orange-red solution was cooled and the solvents were removed in vacuo to afford crude monochlorophosphonate. The residue was taken up in 40 ml of isopropyl alcohol and stirred for 16 h at 22 °C. The solvents were removed in vacuo and the residue was purified by silica gel chromatography, eluting with 10% MeOH/CH_2Cl_2 to give 0.24g (29%) of the title compound.

Mp 96-99 °C. ^1H NMR($CDCl_3$) 8.31(1H, s, H-8), 7.87(1H, s, H-2), 7.19(5H, m, Ph), 5.96(2H, s, NH_2), 4.80 (1H, apparent heptet, J = 6.2, CH), 4.36(2H, t, J = 5.0, H-1'), 3.93(2H, t, J = 5.0, H-2'), 3.86(2H, d, J = 7.9, H-4'), 1.26(3H, d, J = 6.2, CH_3), 1.21(3H, d, J = 6.2 CH_3). ^{13}C NMR ($CDCl_3$) 155.52(C-6), 152.88(C-2), 150.13-(ArC, d, J = 8.3), 149.89(C-4), 141.46(C-8), 129.71(ArC), 125.14(ArC), 120.50(ArC, d, J = 4.5), 119.43(C-5), 72.65(CH, d, J = 7.3), 71.18(C-2', d, J = 10.6), 65.27(C-4', d, J = 167.5), 43.45(C-1'), 23.93(CH_3, d, J = 4.5), 23.82(CH_3, d, J = 4.5). IR(KBr) 3290, 3116, 1670, 1600. MS(Isobutane/DCI) 392(M + H, 100).

Anal. Calcd. for $C_{17}H_{22}N_5O_4P_1$:	C,52.17;	H, 5.66;	N, 17.89.
Found:	C, 52.01;	H, 5.57;	N, 17.64.

EXAMPLE 17

Synthesis of PMEA, (mono-N,N-diethylacetamide, mono pivaloyloxymethyl) ester

To a suspension of 0.100 g (0.239 mmol) of PMEA, mono- N,N-diethylacetamide ester (sodium salt) (Example 27) in 2.5 mL of CH_3CN was added 0.25 mL of Et_3N, whereupon the reaction became homogeneous. To this mixture was added 0.17 mL (1.19 mmol) of chloromethyl pivalate. The reaction was stirred at 22 °C for 24h, evaporated to dryness in vacuo, and purified on a 20 mm flash column. The title compound eluted with 10 % MeOH/CH_2Cl_2 to give 25 mg (21%) of a colorless oil.

^1H NMR ($CDCl_3$) 8.25 (1H, s, H-8), 7.94 (1H, s, H-2), 6.26 (2H, s, NH_2), 5.65 (1H, dd, J = 12.3, 5.4, OCH_2O), 5.60 (1H, dd, J = 12.3, 4.8, OCH_2O), 4.75 (1H, dd, J = 14.7, 10.8, $OCH_2C(O)$), 4.56 (1H, dd, J = 14.5, 14.3, $OCH_2C(O)$), 4.32 (2H, dd, J = 5.7, 4.4, H-1'), 3.97 (2H, d, J = 8.4, H-4'), 3.91 (2H, t, J = 4.8, H-2'), 3.28 (2H, q, J = 7.5, CH_2CH_3), 3.09 (1H, q, J = 7.2, CH_2CH_3), 1.12 (9H, s, $(CH_3)_3$), 1.07 (3H, m, CH_3CH_2), 1.05, (3H, t,

J = 6.9, CH_3CH_2). ^{13}C NMR ($CDCl_3$) 177.85 (C(O)O), 166.25 (C(O)N), 156.34 (C-6), 153.48 (C-2), 150.49 (C-4), 142.22 (C-8), 119.79 (C-5), 81.94 ($(CH_3)_3C$), 81.71 (OCH_2O), 71.55 (C-2', d, J = 10), 65.10 (C-4', d, J = 165), 63.99 (CCH_2OP), 43.53 (C-1'), 41.03 (NCH_2), 40.78 (NCH_2), 27.00 ($(CH_3)_3$), 14.21 (CH_3CH_2), 13.00 (CH_3CH_2). MS (FAB) 501 (M + H, 100). IR 3500-3000, 2978, 1750, 1654, 1600, 1480, 1250.

Anal. Calcd for: $C_{20}H_{33}N_5O_7P \cdot 0.5\ H_2O$	C, 47.15;	H, 6.72;	N, 16.50.
Found:	C, 47.30;	H, 6.58;	N, 16.14.

The following examples were prepared by the methods given in Table I.

EXAMPLE 18

PMEA, cyclic propanyldiester

Mp 195-199 °C. ^1H NMR (d_6-DMSO) 8.13 (1H, s, H-8), 8.12 (1H, s, H-2), 4.35 (2H, t, J = 4.8, H-1'), 4.2 (4H, m, CH_2OP), 3.95 (2H, d, J = 8.8, H-4'), 3.86 (2H, t, J = 4.8, H-2'), 1.98 (1H, m, $CH_2CH_2CH_2$), 1.55 (1H, m, $CH_2CH_2CH_2$). ^{13}C NMR (d_6-DMSO) 156.01 (C-6), 152.48 (C-2), 149.69 (C-4), 141.11 (C-8), 118.68 (C-5), 70.71 (C-2', d, J = 13.8), 68.30 (CH_2OP, d, J = 6.9), 64.55 (C-4', d, J = 158), 42.52 (C-1'), 25.85 ($CH_2CH_2CH_2$, d, J = 9.0). IR (KBr) 3351, 3169, 1660, 1601, 1256, 1063. MS (FAB) 314 (M + H, 100).

Anal. Calcd for: $C_{11}H_{16}N_5O_4P \cdot 1.5\ H_2O$	C, 38.85;	H, 5.63;	N, 20.60.
Found:	C, 38.63;	H, 5.46;	N, 20.49.

EXAMPLE 19

PMEA, bis-diethylamide

Mp 93-96 °C. ^1H NMR (d_6-DMSO) 8.11 (1H, s, H-8), 8.07 (1H, s, H-2), 7.18 (2H, s, NH_2), 4.31 (2H, t, J = 4.8, H-1'), 3.85 (2H, t, J = 4.8, H-2'), 3.68 (2H, d, J = 8.1, H-4'), 2.70 (8H, m, CH_3CH_2), 0.86 (12H, t, J = 7.0, CH_3). ^{13}C NMR (d_6-DMSO) 155.98 (C-6), 152.33 (C-2), 149.63 (C-4), 141.04 (C-8), 118.75 (C-5), 70.30 (C-2', d, J = 13.0), 66.30 (C-4', d, J = 133), 42.63 (C-1'), 37.53 (CH_3CH_2), d, J = 4.1), 13.93 (CH_3, d, J = 1.9). IR (KBr) 3370-2935, 2875, 1680, 1649, 1605, 1211. MS (FAB) 384 (M + H), 100).

Anal. Calcd for: $C_{16}H_{30}N_7O_2P \cdot 0.5\ H_2O$	C, 48.96;	H, 7.96;	N, 24.99.
Found:	C, 48.85;	H, 7.77;	N, 24.92.

EXAMPLE 20

PMEA, isopropyl ester (sodium salt)

Mp 77-85 °C turned to glass and melted over next 40 °C. ^1H NMR (d_6-DMSO) 8.19 (1H, s, H-8), 8.13 (1H, s, H-2), 7.22 (2H, s, NH_2), 4.30 (2H, t, J = 4.4, H-1'), 4.10 (1H, m, OCH), 3.76 (2H, t, J = 4.4, H-2'), 3.31 (2H, d, J = 8.6, H-4'), 0.90 (6H, d, J = 6.0, CH_3). ^{13}C (d_6-DMSO; 90 MHz), 155.90 (C-6), 152.35 (C-2), 149.54 (C-4), 141.39 (C-8), 118.53 (C-5), 70.23 (OCH, d, J = 10), 68.70 (C-4', d, J = 192), 65.55 (C-2', d, J = 5), 42.72 (C-1'), 24.43 (CH_3). IR (Film) 3321, 3163, 1647, 1601, 1578. MS (FAB) 338 (M + H, 70).

Anal. Calcd for: $C_{11}H_{17}N_5O_4P_1Na_1 \cdot H_2O$	C, 37.18;	H, 5.38;	N, 19.71.
Found:	C, 37.11;	H, 5.49;	N, 19.71.

EXAMPLE 21

PMEA, cyclic (2,2-dimethyl)propanyl diester

Mp 224-226 °C. ^{1}H NMR (d_6-DMSO) 8.11 (2H, s, H-8, H-2), 7.21 (2H, s, NH_2), 4.34 (2H, t, J = 5.0, H-1'), 3.99 (2H, d, J = 8.7, H-4'), 3.91 (2H, t, J = 5.0, H-2'), 3.95-3.75 (4H, m, $CH_2C(CH_3)_2CH_2$), 1.06 (3H, s, CH_3), 0.67 (3H, s, CH_3). ^{13}C NMR (d_6-DMSO; 50 MHz) 155.89 (C-6), 152.33 (C-2), 149.53 (C-4), 140.86 (C-8), 118.57 (C-5), 76.67 ($CH_2C(CH_3)_2CH_2$, d, J = 6.8), 70.44 (C-2', d, J = 13.7), 64.43 (C-4', d J = 157), 42.43 (C-1'), 31.70 ($C(CH_3)_2$, d, J = 7.6), 21.05 (CH_3), 19.46 (CH_3). IR (KBr) 3417, 3324, 3152, 2970, 1668, 1650, 1602. MS (FAB) 342 (M + H, 100).

Anal. Calcd for: $C_{13}H_{20}N_5O_4P \cdot 0.25\ H_2O$	C, 45.18;	H, 5.97;	N, 20.27.
Found:	C, 45.58;	H, 6.05;	N, 20.05.

EXAMPLE 22

PMEA, 3-hydroxypropanyl ester, (sodium salt)

^{1}H NMR (d_6-DMSO) 8.17 (1H, s, H-8), 8.11 (1H, s, H-2), 7.20 (2H, s, NH_2), 5.11 (1H, t, OH), 4.28 (2H, t, J = 4.7, H-1'), 3.76 (2H, t, J = 4.7, H-2'), 3.64 (2H, q, J = 6.6, CH_2CH_2OP), 3.41 (2H, d, J = 8.0, H-4'), 3.35 (2H, t, J = 6.2, $HOCH_2$), 1.45 (2H, m, $HOCH_2CH_2$). ^{13}C NMR (d_6-DMSO; 50 MHz) 155.82 (C-6), 152.25 (C-2), 149.43 (C-4), 141.38 (C-8), 118.43 (C-5), 69.77 (C-2', d, J = 10), 67.42 (C-4', d, J = 152), 59.33 (CH_2CH_2OP, d, J = 6), 56.88 ($HOCH_2$), 42.60 (C-1'), 33.91 ($HOCH_2CH_2$; d, J = 4). IR (KBr) 3412, 2956, 1647, 1604, 1482, 1421. MS (FAB) 354 (M + H, 17).

Anal. Calcd for: $C_{11}H_{17}N_5O_5P_1Na_1 \cdot 2.5\ H_2O$	C, 33.17;	H, 5.56;	N, 17.59.
Found:	C, 33.32,	H, 5.28;	N, 17.63.

EXAMPLE 23

PMEA, monooctyl ester

^{1}H NMR (d_5-pyridine) 9.47, 9.34 (2H, 2s, H-2, H-8), 5.46 (2H, t, J = 4.5), 5.3-5.1 (6H, m, H-2', H-4', $CH_2CH_2CH_2O$), 2.68 (2H, m, $CH_2CH_2CH_2O$), 2.33 (2H, m, CH_2CH2CH_2O), 2.1 (8H, m, $CH_3(CH_2)_4$)), 1.79 (3H, t, J = 6.5, CH_3). IR (KBr) 3416, 2928, 1690, 1065. MS (FAB) 386 (M + H, 100).

Anal. Calcd for: $C_{15}H_{28}N_5O_4P \cdot H_2O \cdot Na \cdot 0.6\ NaCl$	C, 41.59;	H, 6.54;	N, 15.15.
Found:	C, 41.80;	H, 6.87;	N, 15.02.

EXAMPLE 24

PMEA, dimethyl ester

Mp 133-135 °C. ^{1}H NMR (d_6-DMSO) 8.14 (1H, s, H-8), 8.10 (1H, s, H-2), 7.29 (2H, s, NH_2), 4.33 (2H, t, J = 5.0, H-1'), 3.90 (2H, d, J = 8.3, H-4'), 3.85 (2H, t, J = 5.0, H-2'), 3.57 (6H, d, J = 10.6, CH_3). ^{13}C NMR (d_6-DMSO) 155.87 (C-6), 152.87 (C-2), 149.59 (C-4), 141.27 (C-8), 118.65 (C-5), 70.40 (C-2', d, J = 11.5), 63.17 (C-4', d, J = 182), 52.79 (CH_3, d, J = 6.4), 42.48 (C-1'). IR (KBr) 3400, 3188, 1671, 1647, 1605. MS (methane/DCI) 302 (M + H, 100)

Anal. Calcd for: $C_{10}H_{15}N_5O_4P \cdot 0.6\ H_2O$	C, 38.43;	H, 5.56;	N, 22.41.
Found:	C, 38.76;	H, 5.45;	N, 22.18.

EXAMPLE 25

PMEA, monomethyl ester, (sodium salt)

^{1}H NMR (d_6-DMSO) 8.19 (1H, s, H-8), 8.11 (1H, s, H-2), 7.17 (2H, s, NH_2), 4.27 (2H, t, J = 5.0, H-1'), 3.77 (2H, t, J = 5.0, H-2'), 3.35 (2H, d, J = 8.0, H-4'), 3.24 (3H, d, J = 10.0, CH_3). ^{13}C (d_6-DMSO; 90 MHz) 155.87 (C-6), 152.26 (C-2), 149.49 (C-4), 141.44 (C-8), 118.51 (C-5), 69.69 (C-2', d, J = 9), 67.09 (C-4', d, J = 152), 50.78 (CH_3, d, J = 5), 42.64 (C-1'). IR (KBr) 3421, 3195, 1649, 1605, 1578, 1516. MS (FAB) 310 (M + H, 23).

Anal. Calcd for $C_9H_{13}N_5O_4P_1Na_1 \cdot 3H_2O \cdot NaCl$	C, 25.63;	H, 4.54;	N, 16.61.
Found:	C, 25.39;	H, 4.84;	N, 16.73.

HRMS Calcd	310.0681
Found:	310.0688

EXAMPLE 26

PMEA, mono- 3-amino - 2,2-dimethylpropyl amide

^{1}H NMR (D_2O) 8.13 (1H, s, H-8), 8.11 (1H, s, H-2), 4.36 (2H, t, J = 5, H-1'), 3.90 (2H, t, J = 5, H-2'), 3.53 (2H, d, J = 8.5, H-4'), 2.71 (2H, s, NH_2CH_2), 2.07 (2H, d, J = 9.4, CH_2NH), 0.70 (6H, s, CH_3). ^{13}C NMR (D_2O) 157.25 (C-6), 154.19 (C-2, 150.78 (C-4), 144.73 (C-8), 120.03 (C-5), 72.24 (C-2', d, J = 12.5), 69.63 (C-4', d, J = 143), 50.05 (CH_2NH), 48.41 (H_2NCH_2), 45.53 (C-1'), 35.36 ($C(CH_3)_2$, d, J = 4), 24.09 (CH_3). IR (KBr) 3786, 3381, 1648, 1605, 1478. MS (FAB) 380 (M + H, 20). HR-MS (M + H)

Anal. Calcd for $C_{13}H_{23}N_7O_3P_1Na_1$:	380.1576.
Found:	380.1567.

EXAMPLE 27

PMEA, mono-hydroxy-2,2-dimethylpropyl ester

^{1}H NMR (d_6-DMSO) 8.14 (1H, s, H-8), 8.09 (1H, s, H-2), 7.16 (2H, s, NH_2), 5.84 (1H, t, OH), 4.27 (2H, t, J = 4.9, H-1'), 3.77 (2H, t, J = 4.9, H-2'), 3.33 (2H, d, J = 8.7, H-4'), 3.24 (2H, d, J = 10, $C(CH_3)_2CH_2OP$), 3.00 (2H, d, $HOCH_2$), 0.63 (6H, s, CH_3). ^{13}C NMR (d_6-DMSO, 50 MHz), 155.84 (C-6), 152.21 (C-2), 149.45 (C-4), 141.26 (C-8), 118.48 (C-5), 69.71 (C-2', d, J = 9.2), 68.27 ($C(CH_3)_2CH_2OP$, d, J = 6.2), 67.48 (C-4', d, J = 152), 65.93 ($HOCH_2$), 42.57 (C-1'), 36.71 ($C(CH_3)_2$, d, J = 2.5), 21.35 (CH_3). IR (KBr) 3426, 2960, 2883, 1645, 1478, 1417. MS (FAB) 360 (M + H, 100).

Anal. Calcd. for $C_{13}H_{22}N_5O_5P \cdot 1.3\ H_2O$:	C, 40.77;	H, 6.48;	N, 18.29.
Found:	C, 40.96;	H, 6.16;	N, 17.95

EXAMPLE 28

PMEA, cyclic-2.2-dimethyl-propanyl diamide

^{1}H NMR (d_6-DMSO) 8.11 (1H, s, H-8), 8.10 (1H, s, H-2), 7.18 (2H, s, NH_2), 4.30 (2H, t, J = 5.0, H-1'), 3.83 (2H, t, J = 5.0, H-2'), 3.63 (2H, d, J = 7.5, H-4'), 4.27 (2H, s, NH, NH), 2.65-2.40 (4H, m, $CH_2C(CH_3)_2CH_2$), 0.98 (3H, s, CH_3), 0.64 (3H, s, CH_3). ^{13}C NMR (d_6-DMSO) 156.01 (C-6), 152.42 (C-2), 149.60 (C-4), 141.24 (C-8), 118.68 (C-5), 70.35 (C-2', d, J = 11.2), 68.53 (C-4', d, J = 131), 52.72 ($CH_2C(CH_3)_2CH_2$, d, J = 2.3),

42.78 (C-1'), 30.54 ($C(CH_3)_2$, d, J = 5.6), 24.82 (CH_3), 23.25 (CH_3). IR (KBr) 3100, 2980, 2940, 1650, 1605. MS (FAB) 340 (M + H, 100). HR-MS (M + H)

Anal. Calcd for $C_{13}H_{22}N_7O_2P$:	340.1651.
Found:	340.1647.

EXAMPLE 29

PMEA, N,N'-dimethyl-cyclic propanyl diamide

^1H NMR (d_6-DMSO) 8.08 (2H, s, H-8, H-2), 7.14 (2H, s, NH_2), 4.28 (2H, br s, H-1'), 3.80 (2H, br s, H-2'), 3.73 (2H, dd, J = 7.6, 2.8 H-4'), 2.85-2.60 (4H, m, CH_3NCH_2), 1.8-1.3 (2H, m, $CH_2CH_2CH_2$), 2.36 (3H, d, J = 3, NCH_3), 2.33 (3H, d, J = 3, NCH_3). ^{13}C NMR (d_6-DMSO) 156.02 (C-6), 152.44 (C-2), 149.77 (C-4), 141.09 (C-8), 118.74 (C-5), 70.44 (C-2', d, J = 14), 65.42 (C-4', d, J = 164), 50.22 (NCH_3), 42.85 (C-1'), 34.28 (CH_3NCH_2), 24.79 ($CH_2CH_2CH_2$). IR (KBr) 3300, 3180, 2930, 2877, 1651, 1600. MS (methane/DCl) 340 (M + H, 100).

Anal. Calcd for $C_{13}H_{22}N_7O_2P \cdot 0.9$ HCl:	C, 41.93;	H, 6.22;	N, 26.33.
Found:	C, 42.33;	H, 6.19;	N, 25.93.

HR-MS (M + H) Calcd for $C_{13}H_{22}N_7O_2P$:	340.1651.
Found:	340.1649.

EXAMPLE 30

PMEA, mono-N,N,-diethylacetamide ester

Mp 189-191 °C. ^1H NMR (d_6-DMSO) 8.16 (1H, s, H-8), 8.14 (1H, s, H-2), 7.55 (2H, s, NH_2), 4.80 (2H, d, J = 9.0, $C(O)CH_2O$), 4.31 (2H, t, J = 5.0, H-1'), 4.03 (2H, t, J = 5.0, H-2'), 3.74 (2H, d, J = 8.5, H-4'), 3.22 (2H, q, J = 7, CH_3CH_2), 3.16 (2H, q, J = 7, CH_3CH_2), 1.01 (3H, t, J = 7, CH_3), 1.01 (3H, t, J = 7, CH_3). ^{13}C NMR (CF_3CO_2D; 90 MHz) 166.10 (C = 0), 150.04, 148.67 (C-6, C-4), 144.74, 144.55 (C-2, C-8), 117.96 (C-5), 70.05 (C-2', d, J = 10), 65.37 (C-4', d, J = 162), 62.87 ($C(O)CH_2$, d, J = 5), 43.44 (C-1'), 14.06 (CH_3), 12.91 (CH_3). IR (KBr) 3392, 3093, 1692, 1650, 1515. MS (methane/DCl) 500 (M + H, 30), 132 (100). HR-MS (M + H)

Anal. Calcd for $C_{14}H_{23}N_6O_5P$:	387.1546.
Found:	387.1543.

EXAMPLE 31

PMEA, mono-acetic acid ester

Mp 197-200 °C. ^1H NMR (d_6-DMSO) 8.19 (1H, s, H-8), 8.17 (1H, s, H-2), 7.75 (2H, s, NH_2), 4.34 (2H, d, J = 4, $C(O)CH_2O$), 4.32 (2H, t, J = 5, H-1'), 3.86 (2H, t, J = 5, H-2'), 3.71 (2H, d, J = 8, H-4'). ^{13}C NMR (d_6-DMSO) 177.19 (C = 0, d, J = 7), 156.84 (C-6), 153.72 (C-2), 150.03 (C-4), 144.05 (C-8), 119.44 (C-5), 71.66 (C-2', d, J = 11), 67.39 (C-4', d, J = 157), 64.90 ($C(O)CH_2O$, d, J = 6), 44.59 (C-1'). IR (KBr) 3366, 3109, 1690, 1611, 1516, 1415. MS (FAB) 332 (M + H, 55).

Anal. Calcd for $C_{10}H_{14}N_5O_5P \cdot 0.3\ H_2O$:	C, 35.74;	H, 4.38;	N, 20.85.
Found:	C, 35.41;	H, 4.43;	N, 20.60.

EXAMPLE 32

PMEA, di(butylacetate ester)

Mp 78-80 °C. ^{1}H NMR (d_6-DMSO) 8.11 (1H, s, H-8), 8.06 (1H, s, H-2), 7.18 (2H, s, NH_2), 4.62 (4H, d, J = 11, $C(O)CH_2OP$), 4.31 (2H, t, J = 5.0, H-1'), 4.07 (4H, t, J = 7, $CH_2OC(O)$), 4.00 (2H, d, J = 8, H-4'), 3.90 (2H, t, J = 5, H-2'), 1.54 (4H, apparent quintet, J = 7, $CH_3CH_2CH_2$), 1.31 (4H, apparent hextet, J = 7,7, CH_3CH_2), 0.86 (6H, t, J = 7, CH_3). ^{13}C NMR (d_6-DMSO) 168.16 (C=O, d, J = 4.7), 156.03 (C-6), 152.44 (C-2), 149.59 (C-4), 141.10 (C-8), 118.65 (C-5), 70.58 (C-2', d, J = 10), 64.70 ($CH_2OC(O)$), 64.19 (C-4', d, J = 165), 62.05 (CH_2OP, d, J = 6), 42.45 (C-1'), 30.10 ($CH_3CH_2CH_2$), 18.53 (CH_3CH2), 13.56 (CH_3). IR (KBr) 3339, 3158, 2994, 2962, 1764, 1662, 1600. MS (methane/DCl) 502 (M + H, 100).

Anal. Calcd for $C_{20}H_{32}N_5O_8P$:	C, 47.90;	H, 6.43;	N, 13.97.
Found:	C. 47.94;	H, 6.40;	N, 13.90.

EXAMPLE 33

PMEA, di(ethylacetate ester)

Mp 82-84 °C ^{1}H NMR (d_6-DMSO) 8.11 (1H, s, H-8), 8.06 (1H, s, H-2), 7.16 (2H, s, NH_2), 4.59 (4H, d, J = 11, $C(O)CH_2O$), 4.30 (2H, t, J = 5.0, H-1'), 4.13 (4H, q, J = 7.0, CH_3CH_2), 4.00 (2H, d, J = 8.0, H-4'), 3.98 (2H, t, J = 5.0, H-2'), 1.18 (6H, t, J = 7.0, CH_3). ^{13}C NMR (D_2O) 171.44 (C=O, d, J = 5), 156.90 (C-6), 153.85 (C-2), 150.56 (C-4), 144.66 (C-8), 119.86 (C-5), 73.02 (C-2', d, J = 10.5), 66.12 (C-4', d, J = 166), 64.85 (CH_3CH_2), 64.75 ($C(O)CH_2O$), 45.57 (C-1'), 15.22 (CH_3). IR (KBr) 3296, 3122, 1764, 1667, 1602. MS (methane/DCl) 446 (M + H, 100).

Anal. Calcd for $C_{16}H_{24}N_5O_8P$:	C, 43.15;	H, 5.43;	N, 15.72.
Found:	C, 43.04;	H, 5.33;	N, 15.58.

EXAMPLE 34

PMEA, monophenyl ester (sodium salt)

Mp 223-228 °C. ^{1}H NMR (d_6-DMSO) 8.14 (1H, s, H-8), 8.13 (1H, s, H-2), 7.50 (2H, s, NH_2), 7.25 (2H, t, J = 8, ArH), 7.07 (1H, t, J = 8, ArH), 7.01 (2H, d, J = 8, ArH), 4.33 (2H, t, J = 5, H-1'), 3.89 (2H, t, J = 5, H-2'), 3.73 (2H, d, J = 8, H-4'). ^{13}C NMR (D20; Partial spectrum) 131.46, 126.06 (ArC), 122.27 (ArC, d, J = 3.5), 72.27 (C-2; d, J = 12), 67.68 (C-4', d, J = 160), 46.08 (C-1'). IR (KBr) 3389, 3068, 1693, 1594. MS (FAB) 350 (M + H, 40).

Anal. Calcd for $C_{14}H_{15}N_5O_4P \cdot H_2O \cdot 0.45$ Na:	C, 44.45;	H, 4.81;	N, 18.51.
Found:	C, 44.45;	H, 4.45;	N, 18.45.

EXAMPLE 35

PMEA, diphenyl ester

Mp 103-114 °C. ^{1}H NMR (d_6-DMSO) 8.15 (1H, s, H-8), 8.11 (1H, s, H-2), 7.40 (2H, s, NH_2), 7.34 (4H, t, J = 7,

ArH), 7.20 (2H, t, J = 7, ArH), 7.04 (4H, t, J = 7, ArH), 4.38 (2H, t, J = 5, H-1'), 4.24 (2H, d, J = 8, H-4'), 3.98 (2H, t, J = 5, H-2'). ^{13}C NMR (d_6-DMSO) 155.51 (C-6), 151.77 (C-2), 149.57 (C-4), 141.46 (C-8), 130.02, 125.49, (ArC), 120.56 (ArC, d, J = 4), 118.71 (C-5), 70.58 (C-2', d, J = 12), 63.52 (C-4', d, J = 164), 42.68 (C-1'). IR (KBr) 3270, 3100, 1675, 1646, 1601, 1490. MS (FAB) 426 (M + H, 100).

Anal. Calcd for $C_{20}H_{20}N_5O_4P \cdot 0.25\ H_2O$:	C, 55.87;	H, 4.81;	N, 16.29.
Found:	C, 55.80;	H, 4.65;	N, 15.98.

EXAMPLE 36

PMEA, mono-N,N-diisopropylacetamide ester (sodium salt)

Mp 219-221 °C. ^{1}H NMR (d_6-DMSO) 8.14 (1H, s, H-8), 8.13 (1H, s, H-2), 7.37 (2H, s, NH_2), 4.45 (2H, d, J = 9, CH_2OP), 4.31 (2H, t, J = 5, H-1'), 3.88 (2H, t, J = 5, H-2'), 3.74 (2H, d, J = 8, H-4'), 3.43 (2H, m, CH-(CH_3)$_2$), 1.26 (6H, d, J = 6, CH_3), 1.08 (6H, d, J = 6, CH_3). ^{13}C NMR (d_6-DMSO/D_2O) 170 (C = O), 156.90 (C-6), 153.89 (C-2), 150.35 (C-4), 144.29 (C-8), 119.68 (C-5), 71.89 (C-2', d, J = 12), 67.81 (C-4', d, J = 158), 65.25 (CH_2OP, d, J = 5), 49.72 (CH(CH_3)$_2$), 47.30 (CH(CH_3)$_2$), 45.00 (C-1'), 21.21 (CH_3). IR (KBr) 3425, 2969, 1691, 1643, 1515. MS (FAB) 415 (M + H, 100).

Anal. Calcd for $C_{16}H_{27}N_6O_5P \cdot 0.67\ H_2O \cdot 0.5$ Na:	C, 43.87;	H, 6.52;	N, 19.19.
Found:	C, 43.92;	H, 6.17;	N, 18.79.

EXAMPLE 37

PMEA, di-(p-nitro-benzyl ester)

Mp 190-193 °C. ^{1}H NMR (d_6-DMSO) 8.16 (4H, d, J = 8, ArH), 8.09 (1H, s, H-8), 8.08 (1H, s, H-2), 7.51 (4H, d, J = 8, ArH), 7.17 (2H, s, NH_2), 5.10 (4H, d, J = 8, $ArCH_2O$), 4.32 (2H, t, J = 5, H-1'), 4.07 (2H, d, J = 8, H-4'), 3.90 (2H, t, J = 5, H-2'). ^{13}C NMR (d_6-DMSO) 155.97 (C-6), 152.94 (C-2), 149.62 (C-4), 147.19, 143.96 (ArC), 141.13 (C-8), 128.15, 123.56 (ArC), 118.65 (C-5), 70.62 (C-2', d, J = 7), 65.86 ($ArCH_2O$, d, J = 6), 63.75 (C-4', d, J = 162), 42.49 (C-1'). IR (KBr) 3420, 3268, 3110, 1674, 1642, 1604. MS (FAB) 544 (M + H, 60).

Anal. Calcd for $C_{22}H_{22}N_7O_9P$:	C, 48.63;	H, 4.09;	N, 18.05.
Found:	C, 48.61;	H, 4.01;	N, 18.04.

EXAMPLE 38

PMEA, mono-p-nitro-benzyl ester, (sodium salt)

Mp 230-240 °C. ^{1}H NMR (d_6-DMSO) 8.19 (2H, d, J = 8.6, ArH), 8.12 (1H, s, H-8), 8.11 (1H, s, H-2), 7.54 (2H, d, J = 8.6, ArH), 4.93 (2H, d, J = 7.7, $ArCH_2O$), 4.63 (2H, t, J = 5, H-1'), 4.31 (2H, t, J = 5, H-2'), 3.72 (2H, d, J = 8.6, H-4'). IR (KBr) 3742, 1930, 1692, 1606, 1518. MS (FAB) 409 (M + H, 27).

Anal. Calcd for $C_{15}H_{17}N_6O_6P \cdot 0.75\ H_2O \cdot 0.5$ Na:	C, 41.58;	H, 4.30;	N, 19.40.
Found:	C, 41.37;	H, 3.92;	N, 19.03.

EXAMPLE 39

PMEA, di-(2,2,2-trichloroethyl ester)

Mp 155-157°C. ^{1}H NMR (d_6-DMSO) 8.11 (1H, s, H-8), 8.08 (1H, s, H-2), 7.16 (2H, s, NH_2), 4.68 (2H, d, J = 7, CCl_3CH_2), 4.67 (2H, d, J = 7, CCl_3CH_2), 4.34 (2H, t, J = 5, H-1'), 4.18 (2H, d, J = 8, H-4'), 3.95 (2H, t, J = 5, H-2'). ^{13}C NMR (d_6-DMSO) 156.09 (C-6), 152.59 (C-2), 149.71 (C-4), 141.28 (C-8), 118.75 (C-5), 95.42 (CCl_3, d, J = 8.6), 75.48 (CCl_3CH_2, d, J = 5.7), 70.92 (C-2', d, J = 7), 63.99 (C-4', d, J = 163), 42.72 (C-1'). IR (KBr) 3372, 3334, 3210, 1658, 1604, 1576. MS (methane/DCI) 536 (100), 534 (50), 192 (95).

Anal. Calcd for $C_{12}H_{14}N_5O_{14}PCl_6$:	C, 26.89;	H, 2.63;	N, 13.07.
Found:	C, 26.85;	H, 2.55;	N, 12.86.

EXAMPLE 40

PMEA, mono-(2,2,2-trichloroethyl ester)

Mp 218-225°C. ^{1}H NMR (d_6-DMSO) 8.51 (2H, s, NH2), 8.30, 8.24 (2H, 2s, H-8, H-2), 4.36 (2H, t, J = 5, H-1'), 4.33 (2H, d, J = 6, Cl_3CCH_2), 3.72 (2H, d, J = 8, C-4'), 3.91 (2H, t, J = 5, H-2'). ^{13}C NMR (d_6-DMSO) 153.03 (C-6), 148.91 (C-2), 148.22 (C-4), 142.78 (C-8), 118.27 (C-5), 97.05 (CCl_3), 75.67 (CCl_3CH_2, d, J = 5), 69.99 (C-2', d, J = 10), 66.17 (C-4', d, J = 159), 43.12 (C-1'). IR (KBr) 3424, 1930, 1690, 1614, 1514, 1414. MS (methane/DCI) 404 (M + H, 1), 136 (40), 113 (100).

Anal. Calcd for $C_{10}H_{13}N_5O_4PCl_3 \cdot 0.3\ CCl_3CH_2OH$:	C, 28.34;	H, 3.05;	N, 15.59.
Found:	C, 28.19;	H, 3.17;	N, 15.59.

EXAMPLE 41

PMEA, di-(benzoyloxymethyl ester)

Mp 49-52°C. ^{1}H NMR (d_6-DMSO) 8.09 (1H, s, H-8), 7.99 (1H, s, H-2), 7.92 (4H, d, J = 7, ArH), 7.67 (2H, t, J = 7.5, ArH), 7.49 (2H, t, J = 7.5, ArH), 7.18 (2H, s, NH2), 5.82 (4H, d, J = 13, OCH_2O), 4.22 (2H, t, J = 5, H-1'), 4.04 (2H, d, J = 8, H-4'), 3.82 (2H, d, J = 5, H-2') ^{13}C NMR (d_6-DMSO) 164.35 (C = 0), 156.02 (C-6), 152.45 (C-2), 149.55 (C-4), 140.99 (C-8), 134.22 (ArH), 129.60 (ArH), 128.98 (ArH), 128.35 (ArH), 118.70 (C-5), 70.62 (C-2', d, J = 11.5), 64.17 (C-4', d, J = 163), 42.29 (C-1'). IR (KBr) 3328, 3182, 1739, 1644, 1602. MS (FAB) 542 (M + H, 45).

Anal. Calcd for $C_{24}H_{24}N_5O_6P \cdot 0.66\ H_2O$:	C, 52.09;	H, 4.61;	N, 12.65.
Found:	C, 52.09;	H, 4.36;	N, 12.37.

EXAMPLE 42

PMEA, di-(p-trifluoromethyl benzyl ester)

Mp 115-125°C. ^{1}H NMR (d_6-DMSO) 8.18 (1H, s, H-8), 8.17 (1H, s, H-2), 7.66 (4H, d, J = 8, ArH), 7.47 (4H, d, J = 8, ArH), 7.57 (2H, s, NH2), 5.09 (4H, d, J = 8, $ArCH_2$), 4.35 (2H, t, J = 5, H-1'), 4.04 (2H, d, J = 8, H-4'), 3.91 (2H, t, J = 5, H-2'). ^{13}C NMR (d_6-DMSO) 154.99 (C-6), 151.13 (C-2), 149.44 (C-4), 141.7 (C-8), 141.12 (ArC), 128.63 (CF_3-ArC, q, J = 31.8), 127.93, 125.31 (ArC), 124.17 (CF_3, q, J = 275), 118.53 (C-5), 70.46 (C-2', d, J = 11), 66.14 ($\bar{A}rCH_2$, d, J = 5.5), 63.78 (C-4', d, J = 161), 42.61 (C-1'). IR (KBr) 3292, 3118, 1670, 1602, 1476. MS (FAB) 590 (M + H, 100).

Anal. Calcd for $C_{24}H_{22}N_5O_4PF_5 \cdot 0.5\ H_2O$:	C, 48.17;	H, 3.87;	N, 11.70.
Found:	C, 47.81;	H, 3.55;	N, 11.30.

EXAMPLE 43

PMEA, mono-(2,2-difluoro-3-hydroxy propyl ester)

^1H NMR (d_6-DMSO) 8.20 (2H, s, H-8, H-2), 7.80 (2H, s, NH2), 4.34 (2H, t, J = 5.0, H-1'), 4.04 (2H, dt, J = 13.2, 7.9), CF_2CH_2OP), 3.87 (2H, t, J = 5.0, H-2'), 3.70 (2H, d, J = 8.0, H-4'), 3.60 (2H, t, J = 13, $HOCH_2$). ^{13}C NMR (D_2O/NaOD) 157.34 (C-6), 154.24 (C-2), 150.67 (C-4), 144.72 (C-8), 123.54 (CF_2, t, J = 30), 120.12 (C-5), 72.40 (C-2', d, J = 12), 67.75 (C-4', d, J = 159), 64.94 (CF_2CH_2OP, dt, J = 30, 5), 63.28 ($HOCH_2$, d, J = 27), 45.49 (C-1'). IR (KBr) 3310, 3112, 1694, 1602, 1514. MS (FAB) 368 (M + H, 55). HR-MS (M + H).

Anal. Calcd far $C_{11}H_{16}N_5O_5F_2P$:	368.0935.
Found:	368.0930.

EXAMPLE 44

PMEA, mono-(P-trifluoromethylbenzyl ester)

^1H NMR (d_6-DMSO) 8.13 (2H, s, H-8, H-2), 7.69 (2H, d, J = 8, ArH), 7.49 (2H, d, J = 8, ArH), 7.34 (2H, s, NH_2), 4.92 (2H, d, J = 8, $ArCH_2O$), 4.32 (2H, t, J = 5, C-1'), 3.87 (2H, t, J = 5, H-2'), 3.75 (2H, d, J = 8, H-4'). IR (KBr) 3062, 1696, 1602, 1514, 1418. MS (FAB) 432 (M + H, 80). HR-MS (M + H).

Anal. Calcd for $C_{16}H_{17}N_5O_4PF_3$:	432.1048.
Found:	432.1039.

EXAMPLE 45

PMEA, dibutylamide

Mp 117-119 °C. ^1H NMR (d_6-DMSO) 8.12 (2H, s, H-8, H-2), 7.19 (2H, s, NH_2), 4.29 (2H, t, J = 5, H-1'), 3.82 (2H, t, J = 5, H-2'), 3.83 (2H, s, NH), 3.52 (2H, d, J = 8, H-4'), 2.64 (4H, m, CH_2NH), 1.24 (8H, m, $CH_3CH_2CH_2$), 0.80 (6H, t, J = 7, CH_3). ^{13}C NMR (d_6-DMSO) 155.98 (C-6), 152.61 (C-2), 149.71 (C-4), 141.52 (C-8), 118.65 (C-5), 70.46 (C-2', d, J = 11), 67.28 (C-4', d, J = 131), 42.83 (C-1'), 39.22 ($NHCH_2$), 34.10 ($NHCH_2CH_2$), 19.59 (CH_3CH_2), 13.92 (CH_3). IR 3278, 3242, 2952, 2928, 2872, 1682, 1608. MS (FAB) 384 (M + H, 100).

Anal. Calcd for $C_{16}H_{30}N_7O_2P$:	C, 50.12;	H, 7.89;	N, 25.57.
Found:	C, 49.77;	H, 7.79;	N, 25.30.

EXAMPLE 46

PMEA, di(2-methyl-propyl ester)

Mp 109-110 °C. ^1H NMR(d_6-DMSO) 8.10(1H, S, H-8) 8.05(1H, S, H-2), 7.19(2H, S, NH_2), 4.31(2H, t, J = 5.0, H-1'), 3.87(2H,t,J = 5.0,H-2'), 3.85 (2H,d,J = 8.5,H-4'), 3.61(4H,dt,J = 6.8,1.4,CH_2OP), 1.72(2H, apparent heptet, J = 6.7,CH), 0.77(12H,d,J = 6.7,CH_3). ^{13}C NMR (d_6-DMSO) 156.04(C-6), 152.42(C-2), 149.60(C-4), 141.05-(C-8), 118.69(C-5), 71.42(CH_2OP, d, J = 6.7), 70.36(C-2',d,J = 11.6), 63.65(C-4',d,J = 163), 42.52(C-1'), 28.72-(CH,d,J = 5.7), 18.45(CH_3). IR(KBr) 3286, 3104, 2960, 1670, 1600. MS(FAB) 386(M + H, 100).

Anal. Calcd for $C_{16}H_{23}N_5O_4P_1$:	C, 49.86;	H, 7.32;	N, 18.17.
Found:	C, 49.81;	H, 7.26;	N, 18.11

EXAMPLE 47

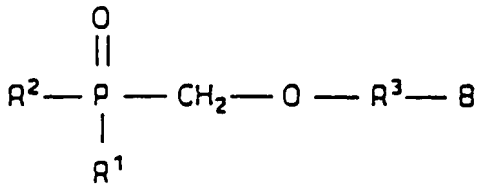
PMEA, di-(3-methyl-butyl) ester

Mp 94-98°C. ^{1}H NMR($CDCl_3$) 8.30(1H, S, H-8) 7.94(1H, S, H-2), 6.21(2H, S, NH_2), 4.37(2H, t, J = 5.0, H-1'), 4.01(4H,dt, J = 6.8, 6.8, CH_2OP), 3.91(2H, t, J = 5.0, H-2'), 3.75(2H,d,J = 8.0,H-4'), 1.63 (2H, apparent heptet, J = 6.6, CH), 1.47(4H,dt, J = 6.7, 6.7, CH_2CH_2OP), 0.84(12H,d,J = 6.5,CH_3). ^{13}C NMR ($CDCl_3$) 155.28(C-6), 152.38(C-2), 150.38(C-4), 141.70(C-8), 119.76(C-5), 71.13(C-2',d,J = 10.0), 65.17(C-4',d,J = 166), 65.02 (CH_2OP,d,J = 6.8), 43.46(C-1'), 39.19 (CH_2CH_2OP,d,J = 5.7), 24.50(CH), 22.31(CH_3), 22.29(CH_3). IR(KBr) 3282, 3106, 2958, 1672, 1600, 1478. MS(methane/DCI) 414(M + H,100).

Anal. Calcd. for $C_{18}H_{32}N_5O_4P_1 \cdot 0.75H_2O$:	C, 50.63;	H, 7.91;	N, 16.40.
Found:	C, 50.67;	H, 7.66;	N, 16.26.

Claims

1. A compound having the structural formula I



FORMULA I

wherein

B represents adenine (A), cytosine (C), guanine (G), thymine (T), Uracil (U), 2,6-diamino purine (DAP), hypoxanthine (Hx), or Z;

R^1 and R^2 are identical or different and independently of one another are each OR^4, NH_2, NHR^5, or $N(R^5)_2$; in some cases, R^1 and R^2 are linked with each other to form a cyclic group, in other cases, R^1 or R^2 is linked to R^3 to form a cyclic group;

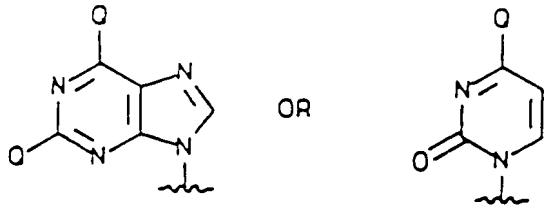
R^3 represents C_1 - C_{20} alkyl which may be substituted or unsubstituted by substituents independently selected from the group consisting of hydroxy, oxygen, nitrogen and halogen; when R^3 is $CH(CH_2OR^6)CH_2$, R^1 and R^2 each independently represent OH, and R^6 is a hydrolyzable ester group;

R^4 represents a physiologically hydrolyzable ester group such as $CH_2C(O)NR^5{}_2$, $CH_2C(O)OR^5$, $CH_2OC(O)R^5$, $CH(R^5)OC(O)R^5$ (R, S, or RS stereochemistry), $CH_2C(R^5)_2CH_2OH$, or CH_2OR^5; R^4 may also be $R^{5'}$ provided that R^4 and $R^{5'}$ are not simultaneously alkyl;

R^5 represents C_1 - C_{20} alkyl, aryl or aryl-alkyl which may be substituted or unsubstituted by substituents independently selected from the group consisting of hydroxy, oxygen, nitrogen and halogen;

$R^{5'}$ represents C_4 - C_{20} alkyl, aryl or aryl-alkyl which may be substituted or unsubstituted by substituents independently selected from the group consisting of hydroxy, oxygen, nitrogen and halogen; and

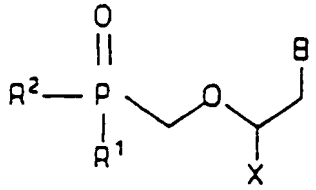
Z is independently chosen from



wherein

Q is independently chosen from H, Cl, NHR^5, NR^5_2, $NHC(O)R^5$, $N(C(O)R^5)_2$, OH or $NCHN(R^5)_2$.

2. The compound of claim 1 which has the general structural formula II



FORMULA II

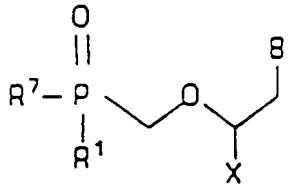
wherein

B, R^1 and R^2 are as described in claim 1, provided that when Q is $NCHN(R^5)_2$, then R^5 is not CH_3;

X represents hydrogen, methyl, CH_2OR^6 (R;S; or RS stereochemistry), hydroxymethyl or substituted or unsubstituted lower alkyl; when X is CH_2OR^6, R^1 and R^2, may additionally be independently chosen from OH; and

R^6 is a hydrolyzable group, provided that when X is CH_2OR^6, R^6 is not CH_2Ph, and R^1 and R^2 are not both ethoxy, further provided that when R^1 is methoxy and R^2 is hydrogen, R^6 is not methyl, and further provided that when R^1 is methoxy and R^2 is hydrogen, R^6 is not octyl.

3. The compound of claim 1 which has the general structural formula III



FORMULA III

wherein

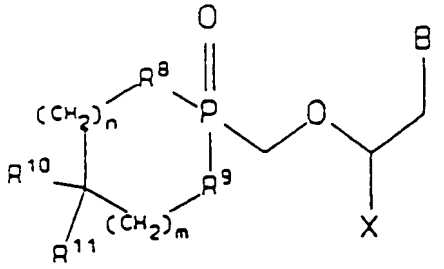
B, and R^1 are as previously described in claim 1;

X is as described in Claim 1;

R^7 represents OH, NH_2, NHR^5, or NR^5_2; and

R^5 is as described in claim 1.

4. The compound of claim 1 which has the general structural formula IV

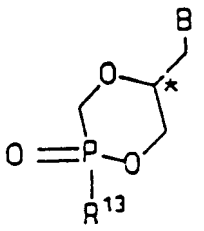


FORMULA IV

wherein

R^8 and R^9 are identical or different and independently of one another are each NR^{12}, or oxygen;
R^{10} and R^{11} are identical or different and independently of one another are each hydrogen, or R^5;
R^{12} represents hydrogen or a lower alkyl;
m and n are identical or different and independently of one another are each 0 or 1;
B and R^5 are as described in claim 1; and
X is as described in claim 2.

5. The compound of claim 1 which has the general structural formula V



* stereochemistry is R, S, or RS

FORMULA V

wherein

R^{13} represents OR^4, NHR^5, NR^5_2, or OH, provided that R^{13} is not OH when B is A or C; and
B, R^4, and R^5 are as described in claim 1.

6. A process for producing the compound of claim 1 which comprises reacting the phosphonate with an activating agent, then reacting with the appropriate amine or alcohol; or alkylation of the phosphonate with the appropriate alkyl halide; or hydrolysis of the diethers or diamines.

7. A process for producing the compound of claim 2 which comprises reacting the phosphonate with an activating agent, then reacting with the appropriate amine or alcohol; or alkylation of the phosphonate with the appropriate alkyl halide; or hydrolysis of the diethers or diamines.

8. A process for producing the compound of claim 3 which comprises reacting the phosphonate with an activating agent, then reacting with the appropriate amine or alcohol; or hydrolysis of the diethers or diamines.

9. A process for producing the compound of claim 4 which comprises reacting the phosphonate with an activating agent, then reacting with the appropriate amine or alcohol.

10. A process for producing the compound of claim 5 which comprises reacting the phosphonate with an activating agent, then reacting with the appropriate amine or alcohol; or alkylation of the phosphonate with the appropriate alkyl halide.

11. The compound of claim 2 which is PMEA, (mono isopropyl, mono pivaloyloxymethyl) ester;
PMEA, di-(propionyloxymethyl ester);
PMEA, di-(isobutyryloxymethyl ester);
PMEA, (mono ethyl, mono isobutyryloxymethyl) ester;
PMEA, (mono isopropyl, monophenyl) ester;
PMEA, bis-diethylamide;
PMEA, di(butylacetate ester);
PMEA, di-(ethylacetate ester);
PMEA, diphenyl ester;
PMEA, di-(p-nitro-benxyl ester);
PMEA, di-(2,2,2-trichloroethyl ester;
PMEA, di-(benzoyloxymethyl ester;
PMEA, di-(p-trifluoromethyl benzyl ester;
PMEA, dibutylamide;
PMEA, di(2-methyl-propyl ester);
PMEA, di-(3-methyl-butyl) ester.

12. The compound of claim 3 which is PMEA di(pivaloyloxymethyl ester);
PMEA, monocholine ester;
PMEA, mono pivaloyloxymethyl ester;
PMEA, (mono-N,N-diethylacetamide, mono pivaloyloxymethyl) ester;
PMEA, 3-hydroxypropanyl ester;
PMEA, monooctyl ester;
PMEA, mono-3-amino-2,2-dimethylpropyl amide;
PMEA, mono-hydroxy-2,2-dimethylpropyl ester;
PMEA, mono-N,N-diethylacetamide ester;
PMEA, mono-acetic acid ester;
PMEA, monophenyl ester;
PMEA, mono-N,N-diisopropylacetamide ester;
PMEA, mono-p-nitro-benxyl ester;
PMEA, mono-(2,2,2-trichloroethyl ester;
PMEA, mono-(2,2-difluoro-3-hydroxy propyl ester);
PMEA, mono-(p-trifluoromethylbenzyl ester).

13. The compound of claim 4 which is PMEA, cyclic propanyldiester;
PMEA, cyclic (2,2-dimethyl)propanyl diester;
PMEA, cyclic-2,2-dimethyl-propanyl diamide;
PMEA, N,N'-dimethyl-cyclic propanyl diamide.

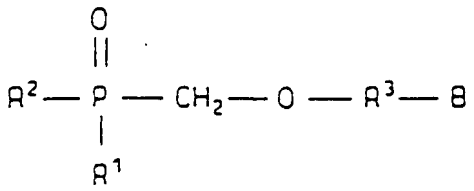
14. A compound of claim 1 - 13 for use in the treatment of viral infection in a mammal which comprises administering an antiviral effective nontoxic dose of one of said substances to the said mammal.

15. A compound of claim 1 - 13 for use in inhibiting growth of a tumor in a mammal which comprises administering to said mammal bearing a tumor a substantially nontoxic antitumor dose of at least one compound of claim 1 - 13.

16. A pharmaceutical composition which comprises at least one compound of claim 1 - 13 in association with a pharmaceutically acceptable substantially nontoxic carrier or excipient.

Claims for the following Contracting State : ES

1. A process for producing a compound having the structural formula I



FORMULA I

wherein

B represents adenine (A), cytosine (C), guanine (G), thymine (T), Uracil (U), 2,6-diamino purine (DAP), hypoxanthine (Hx), or Z;

R^1 and R^2 are identical or different and independently of one another are each OR^4, NH_2, NHR^5, or $N(R^5)_2$; in some cases, R^1 and R^2 are linked with each other to form a cyclic group, in other cases, R^1 or R^2 is linked to R^3 to form a cyclic group;

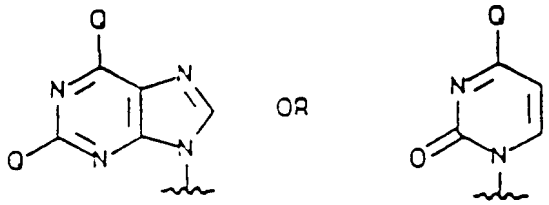
R^3 represents C_1 - C_{20} alkyl which may be substituted or unsubstituted by substituents independently selected from the group consisting of hydroxy, oxygen, nitrogen and halogen; when R^3 is $CH(CH_2OR^6)CH_2$, R^1 and R^2 each independently represent OH, and R^6 is a hydrolyzable ester group;

R^4 represents a physiologically hydrolyzable ester group such as $CH_2C(O)NR^5{}_2$, $CH_2C(O)OR^5$, $CH_2OC(O)R^5$, $CH(R^5)OC(O)R^5$ (R, S, or RS stereochemistry), $CH_2C(R^5)_2CH_2OH$, or CH_2OR^5; R^4 may also be $R^{5'}$ provided that R^4 and $R^{5'}$ are not simultaneously alkyl;

R^5 represents C_1 - C_{20} alkyl, aryl or aryl-alkyl which may be substituted or unsubstituted by substituents independently selected from the group consisting of hydroxy, oxygen, nitrogen and halogen;

$R^{5'}$ represents C_4 - C_{20} alkyl, aryl or aryl-alkyl which may be substituted or unsubstituted by substituents independently selected from the group consisting of hydroxy, oxygen, nitrogen and halogen; and

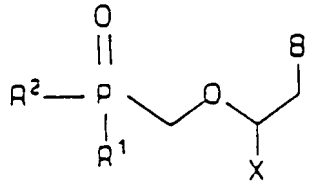
Z is independently chosen from



wherein

Q is independently chosen from H, Cl, NHR^5, $NR^5{}_2$, $NHC(O)R^5$, $N(C(O)R^5)_2$, OH or $NCHN(R^5)_2$, which process comprises reacting the phosphonate with an activating agent, then reacting with the appropriate amine or alcohol; or alkylation of the phosphonate with the appropriate alkyl halide; or hydrolysis of the diethers or diamines.

2. A process for producing a compound having the structural formula II



FORMULA II

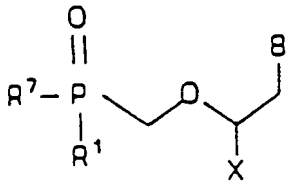
wherein

B, R^1 and R^2 are as described in claim 1, provided that when Q is $NCHN(R^5)_2$, then R^5 is not CH_3;

X represents hydrogen, methyl, CH_2OR^6 (R;S; or RS stereochemistry), hydroxymethyl or substituted or unsubstituted lower alkyl; when X is CH_2OR^6, R^1 and R^2, may additionally be independently chosen from OH; and

R^6 is a hydrolyzable group, provided that when X is CH_2OR^6, R^6 is not CH_2Ph, and R^1 and R^2 are not both ethoxy, further provided that when R^1 is methoxy and R^2 is hydrogen, R^6 is not methyl, and further provided that when R^1 is methoxy and R^2 is hydrogen, R^6 is not octyl, which process comprises reacting the phosphonate with an activating agent, then reacting with the appropriate amine or alcohol; or alkylation of the phosphonate with the appropriate alkyl halide; or hydrolysis of the diethers or diamines.

3. A process for producing a compound having the structural formula III



FORMULA III

wherein

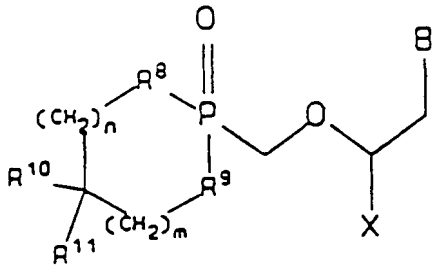
B, and R^1 are as previously described in claim 1;

X is as described in Claim 2;

R^7 represents OH, NH_2, NHR^5, or $NR^5{}_2$; and

R^5 is as described in claim 1, which process comprises reacting the phosphonate with an activating agent, then reacting with the appropriate amine or alcohol; or hydrolysis of the diethers or diamines.

4. A process for producing a compound having the structural formula IV



FORMULA IV

wherein

R^8 and R^9 are identical or different and independently of one another are each NR^{12}, or oxygen;

R^{10} and R^{11} are identical or different and independently of one another are each hydrogen, or R^5;

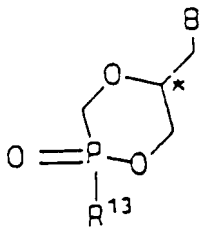
R^{12} represents hydrogen or a lower alkyl;

m and n are identical or different and independently of one another are each 0 or 1;

B and R^5 are as described in claim 1; and

X is as described in claim 2, which procress comprises reacting the phosphonate with an activating agent, then reacting with the appropriate amine or alcohol.

5. A process for producing a compound having the structural formula V



* stereochemistry is R, S, or RS

FORMULA V

wherein

R^{13} represents OR^4, NHR^5, NR^5_2, or OH, provided that R^{13} is not OH when B is A or C; and

B, R^4 and R^5 are as described in claim 1, which process comprises reacting the phosphonate with an activating agent, then reacting with the appropriate amine or alcohol; or alkylation of the phosphonate with the appropriate alkyl halide.

6. A process according to claim 2 for producing the following compounds: PMEA, (mono isopropyl, mono pivaloyloxymethyl) ester;
PMEA, di-(propionyloxymethyl ester);
PMEA, di-(isobutyryloxymethyl ester);
PMEA, (mono ethyl, mono isobutyryloxymethyl) ester;
PMEA, (mono isopropyl, monophenyl) ester;
PMEA, bis-diethylamide;
PMEA, di(butylacetate ester);
PMEA, di-(ethylacetate ester);
PMEA, diphenyl ester;
PMEA, di-(p-nitro-benxyl ester);
PMEA, di-(2,2,2-trichloroethyl ester;
PMEA, di-(benzoyloxymethyl ester;
PMEA, di-(p-trifluoromethyl benzyl ester;
PMEA, dibutylamide;
PMEA, di(2-methyl-propyl ester);
PMEA, di-(3-methyl-butyl) ester.

7. A process according to claim 3 for producing the following compounds: PMEA di(pivaloyloxymethyl ester);
PMEA, monocholine ester;
PMEA, mono pivaloyloxymethyl ester;
PMEA, (mono-N,N-diethylacetamide, mono pivaloyloxymethyl) ester;
PMEA, 3-hydroxypropanyl ester;
PMEA, monooctyl ester;
PMEA, mono-3-amino-2,2-dimethylpropyl amide;
PMEA, mono-hydroxy-2,2-dimethylpropyl ester;
PMEA, mono-N,N-diethylacetamide ester;
PMEA, mono-acetic acid ester;
PMEA, monophenyl ester;
PMEA, mono-N,N-diisopropylacetamide ester;
PMEA, mono-p-nitro-benxyl ester;
PMEA, mono-(2,2,2-trichloroethyl ester;

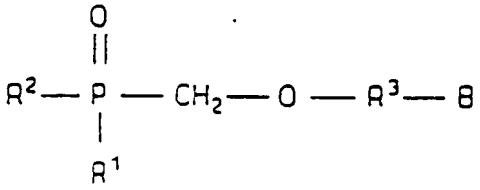
PMEA, mono-(2,2-difluoro-3-hydroxy propyl ester);
PMEA, mono-(p-trifluoromethylbenzyl ester).

8. A process according to claim 4 for producing the following compounds: PMEA, cyclic propanyldiester;
PMEA, cyclic (2,2-dimethyl)propanyl diester;
PMEA, cyclic-2,2-dimethyl-propanyl diamide;
PMEA, N,N'-dimethyl-cyclic propanyl diamide.

9. A process for preparing a pharmaceutical composition which comprises mixing an amount of at least one compound as defined in claim 1 - 8, or combination thereof, with a pharmaceutically acceptable substantially nontoxic carrier or excipient.

Claims for the following Contracting State GR

1. A compound having the structural formula I



FORMULA I

wherein

B represents adenine (A), cytosine (C), guanine (G), thymine (T), Uracil (U), 2,6-diamino purine (DAP), hypoxanthine (Hx), or Z;

R^1 and R^2 are identical or different and independently of one another are each OR^4, NH_2, NHR^5, or $N(R^5)_2$; in some cases, R^1 and R^2 are linked with each other to form a cyclic group, in other cases, R^1 or R^2 is linked to R^3 to form a cyclic group;

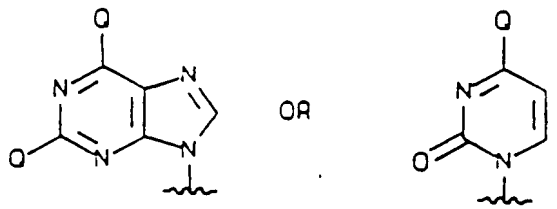
R^3 represents C_1 - C_{20} alkyl which may be substituted or unsubstituted by substituents independently selected from the group consisting of hydroxy, oxygen, nitrogen and halogen; when R^3 is $CH(CH_2OR^6)CH_2$, R^1 and R^2 each independently represent OH, and R^6 is a hydrolyzable ester group;

R^4 represents a physiologically hydrolyzable ester group such as $CH_2C(O)NR^5{}_2$, $CH_2C(O)OR^5$, $CH_2OC(O)R^5$, $CH(R^5)OC(O)R^5$ (R, S, or RS stereochemistry), $CH_2C(R^5)_2CH_2OH$, or CH_2OR^5; R^4 may also be $R^{5'}$ provided that R^4 and $R^{5'}$ are not simultaneously alkyl;

R^5 represents C_1 - C_{20} alkyl, aryl or aryl-alkyl which may be substituted or unsubstituted by substituents independently selected from the group consisting of hydroxy, oxygen, nitrogen and halogen;

$R^{5'}$ represents C_4 - C_{20} alkyl, aryl or aryl-alkyl which may be substituted or unsubstituted by substituents independently selected from the group consisting of hydroxy, oxygen, nitrogen and halogen; and

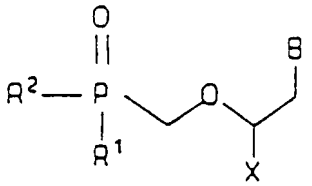
Z is independently chosen from



wherein

Q is independently chosen from H, Cl, NHR^5, $NR^5{}_2$, $NHC(O)R^5$, $N(C(O)R^5)_2$, OH or $NCHN(R^5)_2$.

2. The compound of claim 1 which has the general structural formula II



FORMULA II

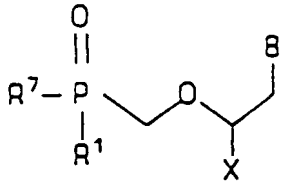
wherein

B, R^1 and R^2 are as described in claim 1, provided that when Q is $NCHN(R^5)_2$, then R^5 is not CH_3;

X represents hydrogen, methyl, CH_2OR^6 (R;S; or RS stereochemistry), hydroxymethyl or substituted or unsubstituted lower alkyl; when X is CH_2OR^6, R^1 and R^2, may additionally be independently chosen from OH; and

R^6 is a hydrolyzable group, provided that when X is CH_2OR^6, R^6 is not CH_2Ph, and R^1 and R^2 are not both ethoxy, further provided that when R^1 is methoxy and R^2 is hydrogen, R^6 is not methyl, and further provided that when R^1 is methoxy and R^2 is hydrogen, R^6 is not octyl.

3. The compound of claim 1 which has the general structural formula III



FORMULA III

wherein

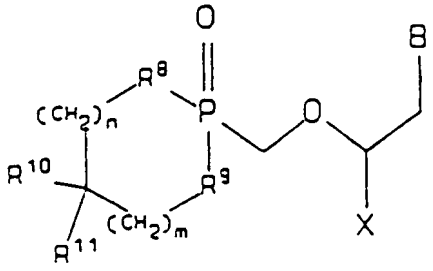
B, and R^1 are as previously described in claim 1;

X is as described in Claim 1;

R^7 represents OH, NH_2, NHR^5, or $NR^5{}_2$; and

R^5 is as described in claim 1.

4. The compound of claim 1 which has the general structural formula IV



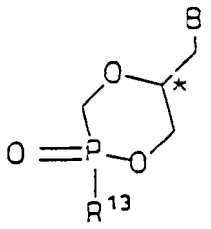
FORMULA IV

wherein

R^8 and R^9 are identical or different and independently of one another are each NR^{12}, or oxygen;

R^{10} and R^{11} are identical or different and independently of one another are each hydrogen, or R^5;
R^{12} represents hydrogen or a lower alkyl;
m and n are identical or different and independently of one another are each 0 or 1;
B and R^5 are as described in claim 1; and
X is as described in claim 2.

5. The compound of claim 1 which has the general structural formula V



* stereochemistry is R, S, or RS

FORMULA V

wherein
R^{13} represents OR^4, NHR^5, NR^5_2, or OH, provided that R^{13} is not OH when B is A or C; and
B, R^4, and R^5 are as described in claim 1.

6. A process for producing the compound of claim 1 which comprises reacting the phosphonate with an activating agent, then reacting with the appropriate amine or alcohol; or alkylation of the phosphonate with the appropriate alkyl halide; or hydrolysis of the diethers or diamines.

7. A process for producing the compound of claim 2 which comprises reacting the phosphonate with an activating agent, then reacting with the appropriate amine or alcohol; or alkylation of the phosphonate with the appropriate alkyl halide; or hydrolysis of the diethers or diamines.

8. A process for producing the compound of claim 3 which comprises reacting the phosphonate with an activating agent, then reacting with the appropriate amine or alcohol; or hydrolysis of the diethers or diamines.

9. A process for producing the compound of claim 4 which comprises reacting the phosphonate with an activating agent, then reacting with the appropriate amine or alcohol.

10. A process for producing the compound of claim 5 which comprises reacting the phosphonate with an activating agent, then reacting with the appropriate amine or alcohol; or alkylation of the phosphonate with the appropriate alkyl halide.

11. The compound of claim 2 which is PMEA, (mono isopropyl, mono pivaloyloxymethyl) ester;
PMEA, di-(propionyloxymethyl ester);
PMEA, di-(isobutyryloxymethyl ester);
PMEA, (mono ethyl, mono isobutyryloxymethyl) ester;
PMEA, (mono isopropyl, monophenyl) ester;
PMEA, bis-diethylamide;
PMEA, di(butylacetate ester);
PMEA, di-(ethylacetate ester);
PMEA, diphenyl ester;
PMEA, di-(p-nitro-benxyl ester);

PMEA, di-(2,2,2-trichloroetnyl ester;
PMEA, di-(benzoyloxymethyl ester;
PMEA, di-(p-trifluoromethyl benzyl ester;
PMEA, dibutylamide;
PMEA, di(2-methyl-propyl ester);
PMEA, di-(3-methyl-butyl) ester.

12. The compound of claim 3 which is PMEA di(pivaloyloxymethyl ester);
PMEA, monocholine ester;
PMEA, mono pivaloyloxymethyl ester;
PMEA, (mono-N,N-diethylacetamide, mono pivaloyloxymethyl) ester;
PMEA, 3-hydroxypropanyl ester;
PMEA, monooctyl ester;
PMEA, mono-3-amino-2,2-dimethylpropyl amide;
PMEA, mono-hydroxy-2,2-dimethylpropyl ester;
PMEA, mono-N,N-diethylacetamide ester;
PMEA, mono-acetic acid ester;
PMEA, monophenyl ester;
PMEA, mono-N,N-diisopropylacetamide ester;
PMEA, mono-p-nitro-benxyl ester;
PMEA, mono-(2,2,2-trichloroethyl ester;
PMEA, mono-(2,2-difluoro-3-hydroxy propyl ester);
PMEA, mono-(p-trifluoromethylbenzyl ester).

13. The compound of claim 4 which is PMEA, cyclic propanyldiester;
PMEA, cyclic (2,2-dimethyl)propanyl diester;
PMEA, cyclic-2,2-dimethyl-propanyl diamide;
PMEA, N,N'-dimethyl-cyclic propanyl diamide.

14. A compound of claim 1 - 13 for use in the treatment of viral infection in a mammal which comprises administering an antiviral effective nontoxic dose of one of said substances to the said mammal.

15. A compound of claim 1 - 13 for use in inhibiting growth of a tumor in a mammal which comprises administering to said mammal bearing a tumor a substantially nontoxic antitumor dose of at least one compound of claim 1 - 13.

16. A process for preparing a pharmaceutical composition which comprises mixing at least one compound of claim 1 - 13 with a pharmaceutically acceptable substantially nontoxic carrier or excipient.

European Patent Office

PARTIAL EUROPEAN SEARCH REPORT

which under Rule 45 of the European Patent Convention shall be considered, for the purposes of subsequent proceedings, as the European search report

Application number

EP 91115312

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
X	EP-A-0269947 (BRISTOL-MYERS COMPANY) * claims 1,7 *	11,12	C07F9/6561 C07F9/6512 C07F9/6574 C07F9/6584 A61K31/675
D,X	EP-A-0270885 (BRISTOL-MYERS COMPANY) * claim 11; page 6, lines 2,3 *	11,12	
D,A	EP-A-0205826 (STICHTING REGA V.Z.W.) * claim 1 *	5	
A	CHEMICAL ABSTRACTS vol. 112, no. 19, 7 May 1990, abstract no. 179685h, Columbus, Ohio, US; A. HOLY et al.: "Synthesis of N-(2-Phosphonyl-methoxyethyl) derivatives of hetero-cyclic bases"	11	
A	CHEMICAL ABSTRACTS vol. 108, no. 21, 23 May 1988, abstract no. 179636k, Columbus, Ohio, US; E. DE CLERCQ et al.: "Antiverial activity of phosphonylmethoxyalkyl derivatives of purines and pyrimidines"	14	

TECHNICAL FIELDS SEARCHED (Int. Cl.5)

C07F9/6561
C07F9/6512
C07F9/6574
C07F9/6584
A61K31/675

INCOMPLETE SEARCH

The Search Division considers that the present European patent application does not comply with the provisions of the European Patent Convention to such an extent that it is not possible to carry out a meaningful search into the state of the art on the basis of some of the claims.

Claims searched completely: 11-13

Claims searched incompletely: 4-10,14-16

Claims not searched: 1-3

Reason for the limitation of the search:

see annex

Place of search	Date of completion of the search	Examiner
BERLIN	18.12.1991	KAPTEYN, H.G.

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

EPO Form 1503.1 03.82

Annex 1

Claim 1: The definition of R^4 is not clear. In the description of the application the meaning of "physiological hydrolizable" is not explained. The alkyl and aryl esters seem to be not within the definition of the physiologically hydrolizable esters, because they are alternatively claimed with $R^{3'}$. On the other side it is claimed that they can not be simultaneously alkyl. That means they can be alternatively alkyl. The definitions of R^3, R^5 and $R^{5'}$ are not correct. A substituent nitrogen does not exist.

Claim 2: The definition of R^6 in claim 2 is broader than the definition of claim 1, but claim 2 shall be dependent from claim 1. This is a contradiction. The definitions of R^1 and R^2 are not correct. Following claim 1 they can not be H, methoxy or ethoxy. They can only be OH if R^6 is an ester group. This too is in contradiction with claim 1.

Claim 3: The group X is not described in claim 1 as is stated in claim 3. The description of X in claim 2 is not in the scope of claim 1. Therefore the meaning of X is not clear. The definition of R^7 is broader than the correspondend R^2 in claim 1, but claim 3 shall be dependent from claim 1. This is a contradiction.

Claim 4: Claim 4: is searched with the exception of R^5 beeing nitrogen

Claim 5: Since the meaning of R^4 in claim 1 is not clear the search was limited to the examples given for R^4 and the definitions for $R^{5'}$ with exception of the substituent nitrogen.

Claims 6-10: Claims 6-10 are partially searched in the scope of the claims 4, 5 and 11-13.

Claims 14-16: Claims 14-16 are partially searched in the scope of claims 4, 5 and 11-13.